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THE DECLINE OF RHEUMATIC FEVER. RECURRENCE RATES OF RHEUMATIC FEVER AMONG 782 CHILDREN FOR TWENTY-ONE CONSECUTIVE CALENDAR YEARS (1936-1956)

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INTRODUCTION

THERE has been a notable decrease in the incidence, morbidity, and mortality of infectious diseases during the past two decades. A decline in the incidence, morbidity, and mortality of rheumatic fever has been reported in several studies in Great Britain, Canada, and the United States. This downward trend is stated to have antedated the antimicrobial era. Some of the influential factors which were considered to have contributed to the apparent downward trend were more accurate differential diagnosis, the control of infectious diseases, and better child care. Many of the more recent reports stress the role of antibiotic therapy. The majority of authors were cognizant of the limitations inherent in epidemiologic studies of rheumatic fever.[1-11]

Reliable data on the incidence, morbidity, and mortality of rheumatic fever or rheumatic heart disease are not as yet available. Two of the most variable factors concern data based on historical information and differences in diagnostic criteria. The limitations of estimates of the prevalence of rheumatic heart disease obtained from school surveys or census data are well known. In some localities, rheumatic fever is reportable and the registry of rheumatic heart

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disease is being attempted. Hitchens,[8] in a comprehensive study based on referral of children from the school population in Cardiff, Wales, with about 70 per cent ascertainment of cases, noted a decline in "inception rates" starting about 1935.[12] Recurrence rates of rheumatic fever have been utilized more commonly, particularly in the evaluation of therapeutic measures. Analysis of mortality data may of course be misleading due to the well-known inadequacy and inconsistency of death certificates.

In a previous study, age-specific recurrence rates for the years 1916-1943 and recurrence rates for 12 consecutive calendar years (1924-1935) were obtained.[13] To determine whether there has been any change in the past 21 years (1936-1956), and if so to examine some of the possible influential factors, the following investigation was undertaken. Since the diagnostic criteria, and medical and social service supervision, were uniform during the entire 40-year period, any real change in the risk of recurrence should be reflected in the analysis of the data during the past two decades.

MATERIAL AND METHODS

The records analyzed were designed for documentation of the natural history of rheumatic fever.[14] They were consecutive records of 782 children, born after 1916, who were registered in the Cardiac Rheumatic Clinic of The New York Hospital and who had been under uniform, continuous, close medical and social service supervision. There were 370 males and 412 females, and analysis of the observations on them covered a time span from 1936-1956, with an age span of 2 to 20 years.

For the majority of patients, clinic visits were made on a monthly basis and all were encouraged to phone in case of any illness. Over the years, numerous clinical investigations were under way, requiring frequent clinic and home visits.

During the years of observation there has been a general improvement in the standard of living in Greater New York City. To determine whether this was reflected in the clinic population, the socioeconomic status of the patients during the 21 years was evaluated by the *same* social worker who had an intimate knowledge of the living conditions of these patients. Families were grouped into environmental categories as I (good), II (fair), and III (poor), in which family size, income, diet, housing and living conditions, and quality of child care were taken into consideration.

Antimicrobial therapy for respiratory infections was not given routinely until 1952. During the years 1952-1956, the majority of patients who experienced intercurrent febrile respiratory infections received antibiotic therapy. In addition, as part of another investigation, during the years 1952-1956 a group of children who were on continuous oral penicillin prophylaxis for 6 months to 4 years each received 4 to 500,000 units daily.

The diagnosis of rheumatic fever was made in the presence of a major manifestation of rheumatic fever, i.e., carditis, usually associated with polyarthritis, chorea, or subcutaneous nodules. Minor manifestations alone were not included as recurrences.[15]

A modified life table method of analysis was used.[16] Pertinent data were transferred to McBee Keysort punch cards to facilitate analysis. Details of the computations and statistical methods are included in the Appendix.

OBSERVATIONS

Annual Recurrence Rates (1936-1956).—During the 21-year period, 782 children contributing 5,664 person-years of life experience, had 613 recurrent attacks of the major manifestations of rheumatic fever, exclusive of 15 repeat recurrences within a given calendar year, giving a crude over-all rate of 10.8 per cent per year (see Appendix for method). During the period of the study, 55.5 per cent of the children had no recurrences. In Table I and Fig. 1, the annual recurrence rates adjusted for age (Appendix) are presented for 21 consecutive calendar years. The downward slope from 1937-1956 of −0.4 per cent per year, best fitted by the data, is significantly different from zero. The high rate of 1936 was omitted from the calculation of the slope because it was so extremely divergent, but its value is supporting evidence of a downward trend. Analysis restricted to ages 4 to 16, not age adjusted, yielded parallel results. Thus, although there were fluctuations at specific years, there is a definite downward trend in the annual recurrence rates from 1936-1956. The time trend of recurrence rates for 12 consecutive calendar years (1924-1935) was previously analyzed and no significant decline had been found.[13]

TABLE I. AGE-ADJUSTED ANNUAL RHEUMATIC RECURRENCE RATES, AGES 2 TO 20 (1936-1956)

YEAR	PERSON-YEARS (NUMBER)	AGE-ADJUSTED RECURRENCE RATE (PER CENT)
1936	432	20.8
1937	460	12.9
1938	453	12.6
1939	439	14.4
1940	414	13.5
1941	393	14.3
1942	354	5.2
1943	319	7.5
1944	278	8.5
1945	245	11.5
1946	221	6.6
1947	201	10.5
1948	184	11.5
1949	159	12.7
1950	145	6.6
1951	142	7.1
1952	156	8.8
1953	166	6.1
1954	166	6.4
1955	170	5.1
1956	167	4.1
Total	5,664	10.8
Mean rate		9.8

Risk of Recurrence Related to Interval Since Last Attack.—It was found in the earlier study that increasing separation in time from a rheumatic attack significantly decreased the risk of a recurrence.[13]

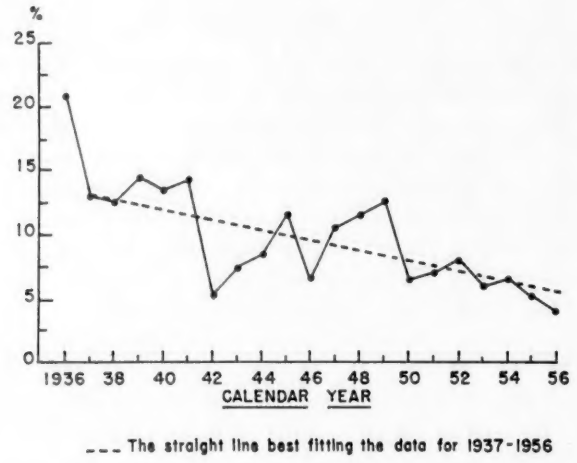

Fig. 1.—Age-adjusted annual recurrence rates for a total of 782 rheumatic children with a total of 5,664 person-years.

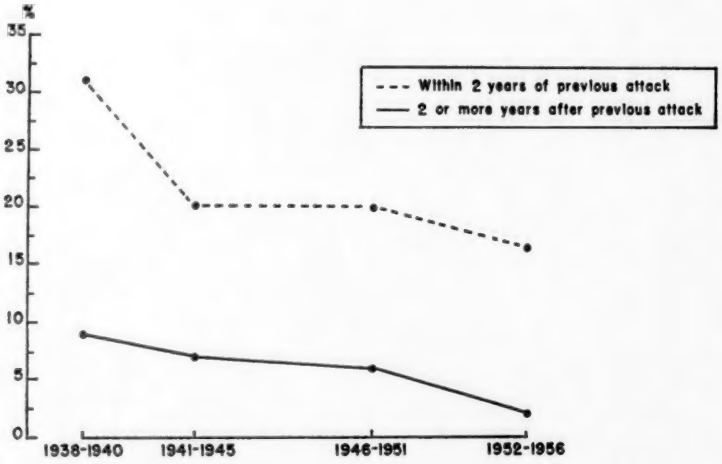

Fig. 2.—Recurrence rates according to interval since last attack for rheumatic children aged 4-16 years, with a total of 2,869 person-years.

Analysis of *observed* recurrence rates, excluding historical data, during 1938-1956 (Appendix) for ages 4-16 showed that the mean annual recurrence rate for those with an attack within 2 years was 21.4 per 100 person-years, three times the mean annual rate of 6 per cent observed in children free from a rheumatic attack for 2 or more years (Table II, Fig. 2). A comparison of four calendar

periods for the high and low risk groups is presented in Fig. 2, showing a significant decline in the recurrence rates over the years in both groups. It is to be noted that during 1952-1956 the rate of 2.2 per cent for those free of rheumatic activity for 2 or more years is less than one-fourth that (9.1 per cent) for the corresponding group during the years 1938-1940. For those children within 2 years of a previous attack the recurrence rate (16.5 per cent) for the years 1952-1956 declined to one-half the earlier rate of 32.2 per cent for 1938-1940.

TABLE II. OBSERVED RECURRENCE RATES FOR RHEUMATIC CHILDREN, AGED 4-16, BY INTERVAL SINCE PREVIOUS ATTACK
(1938-1956)

CALENDAR PERIODS	(A) TWO YEARS OR MORE SINCE LAST ATTACK			(B) LESS THAN TWO YEARS SINCE LAST ATTACK			TOTAL A + B ALL PATIENTS			PER CENT OF P-YRS. WITHIN 2 YEARS OF ATTACK
	(1) P-YRS.	(2) REC.	(3) RATE (%)	(4) P-YRS.	(5) REC.	(6) RATE (%)	(7) P-YRS.	(8) REC.	(9) RATE (%)	(10)
1938–40	508	46	9.1	320.5	103	32.2	828.5	149	18.0	39
1941–45	591	42	7.1	227.0	46	20.2	818.0	88	10.8	28
1946–51	309	19	6.1	218.0	44	20.2	527.0	63	12.0	41
1952–56	371	8	2.2	224.5	37	16.5	595.5	45	7.6	38
Total	1,779	115	6.5	999.0	230	23.2	2,869.0	345	12.0	34
Mean rate*			6.0			21.4			11.6	36

*Mean of 19 consecutive annual rates, 1938-1956.

In the previous study (1916-1943), and for the first 16 years in the present analysis for 1936-1951, the comparative risk of recurrence for the recent rheumatic activity group was rather constantly about three times that for the group free of activity 2 or more years. In the last 5 years, from 1952 to 1956, the observed recurrence rate among the short interval group was seven times that for the group with a longer free interval.

Concern that the decline in annual recurrence rates might have reflected an increasing proportion of children at low risk over the years, proved unfounded. The proportion of high and low risk cases was fairly constant over the years. The entry of new patients at high risk balanced the continuous presence of cases at low risk (Table II).

Age-specific Recurrence Rates.—Variation in susceptibility by age is one of the recognized characteristics of rheumatic fever. The incidence of onsets and recurrences is highest between the ages of 4 to 13. Age-specific recurrence rates for the years 1921-1943 and 1944-1956, presented in Table III and Fig. 3, again reveal rates to be higher before 13 and lower after this age.

At almost every age the recurrence rates were lower during the years 1944 to 1956. The decline among children 6 to 13 years of age was from 25 to 15 per cent, and from 6 to 2.8 per cent for ages 14 to 20. It may be stated that the ap-

TABLE III. AGE-SPECIFIC RECURRENCE RATES IN RHEUMATIC CHILDREN (1921-43 AND 1944-56)

YR. OF AGE	(1921-1943)			(1944-1956)		
	P-YRS.	REC.	RATE (%)	P-YRS.	REC.	RATE (%)
6	188.5	61	32.4	49.5	8	16.2
7	252.0	85	33.7	70.0	10	14.3
8	305.5	96	31.4	92.0	14	15.2
9	356.5	94	26.4	126.0	19	15.1
10	394.5	112	28.4	125.0	30	24.0
11	411.0	102	24.8	139.5	18	13.0
12	410.5	72	17.5	151.5	22	14.5
13	397.0	59	14.9	158.5	17	10.7
6–13	2,715.5	681	25.0	912.0	138	15.1
14	375.0	31	8.3	161.5	5	3.1
15	350.0	33	9.6	168.5	14	8.3
16	323.0	26	8.0	187.5	8	4.3
17	296.5	13	4.4	197.5	3	1.5
18	275.0	7	2.5	228.0	6	2.6
19	250.5	12	4.9	244.5	3	1.2
20	220.0	6	2.7	256.5	2	0.8
14–20	2,090.0	128	6.1	1,444.0	41	2.8

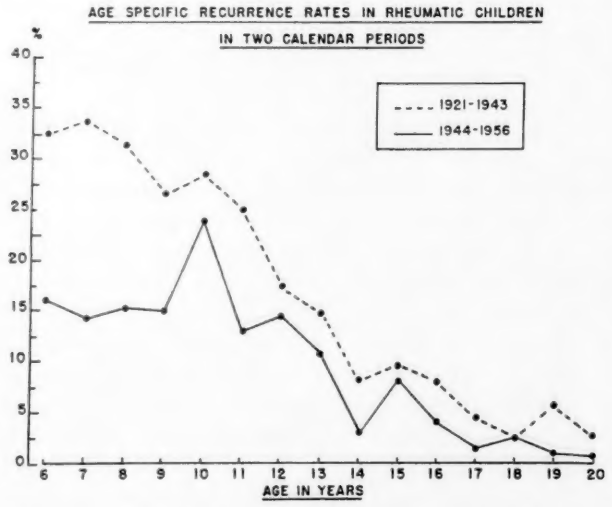

Fig. 3.—Age-specific recurrence rates in two calendar periods, with a total of 2,090 persons-year during 1921-1943, and 1,444 person-years during 1944-1956.

proximate chance of a recurrence in any one year for children aged 6 to 13 declined from 1 in 4 before 1944 to about 1 in 7 between 1944 and 1956; for ages 14 to 20, the chance fell from 1 in 16 to 1 in 35.

Risk of Recurrence Related to Environmental Status.—The general improvement in the standard of living in Greater New York City over the past two

decades was found to be reflected in the socioeconomic composition of the clinic population. Evaluation of the socioeconomic status during the period 1936-1945 revealed that about one-half of the patients were in the poorest environmental group (III); in less than one-half the economic status was considered fair (II), and in only 8 per cent was the environmental status considered good (I). For the period 1945-1951, and particularly for 1952-1956, the relative percentage of patients in the best environmental group increased and those in the poorest environmental group diminished (Table IV, Fig. 4).

TABLE IV. COMPOSITION OF CLINIC POPULATION BY ENVIRONMENTAL STATUS

PERIOD	I: GOOD		II: FAIR		III: POOR		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
1936–1945	50	8	257	42	307	50	614	100
1946–1951	47	16	136	46	114	38	297	100
1952–1956	66	29	94	41	68	30	228	100
*Total pts. observed 1936-1956	106	14	330	42	346	44		

*Total is not the sum of the patients observed during individual periods, because many patients were observed during more than one period.

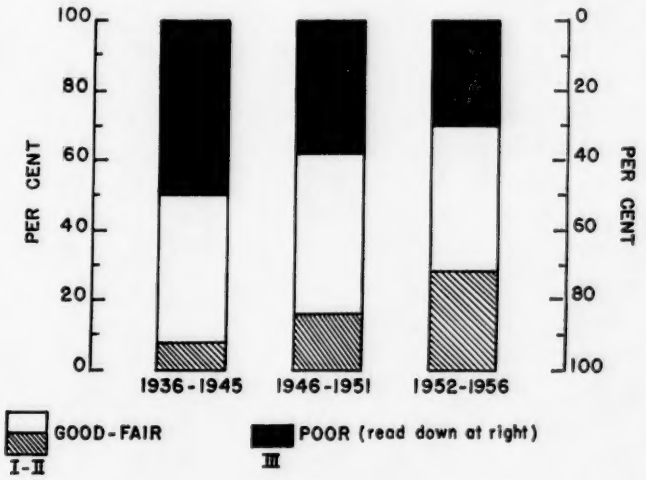

Fig. 4.—Composition of clinic population by environmental status during three calendar periods, including 614 patients from 1936-1945, 297 patients from 1946-1951, and 228 patients from 1952-1956.

Analysis of recurrence rates according to environmental groups revealed rates to be generally lower for I and II, but far more strikingly so during the last 5 years (1952-1956) when the rates for patients aged 4 to 16 in groups I and II fell to less than 4 per cent, while the rates in III which had shown an initial

drop for the years 1936-1951 later rose to 19 per cent (Table V, Fig. 5). In order to determine whether the recurrence rate in group III was influenced by a greater proportion of higher risk patients, i.e., with recent active rheumatic fever, further analysis was made by interval since last attack and environmental group. A difference in recurrence rates according to environmental group was observed for patients at both short and long intervals since previous attack.

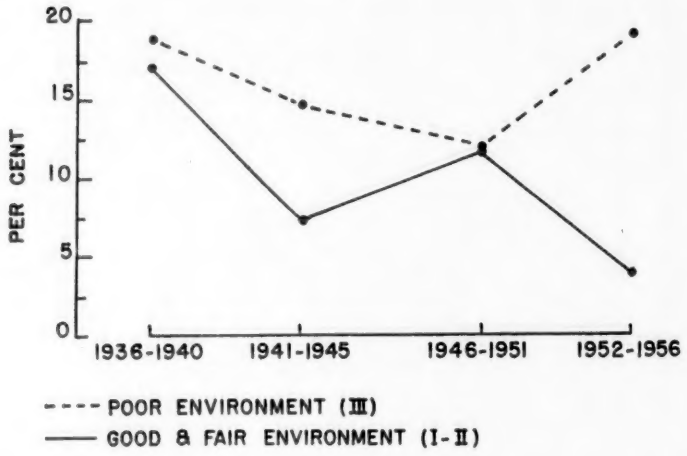

Fig. 5.—Distribution of recurrence rates, with a total of 1,987.5 person-years for good and fair environment, and 1,510.5 person-years for poor environment.

TABLE V. RECURRENCE RATES BY ENVIRONMENTAL STATUS, 1936-1956, AGES 4-16

PERIOD	I AND II, GOOD AND FAIR			III, POOR		
	P-YRS.	REC.	RATE (%)	P-YRS.	REC.	RATE (%)
1936–40	689.0	119	17.3	795.0	149	18.8
1941–45	441.0	32	7.3	381.0	56	14.7
1946–51	403.5	47	11.7	193.5	23	11.9
1952–56	454.0	17	3.8	141.0	27	19.2
Total	1,987.5	215	10.8	1,510.5	255	16.9
Mean			10.0			16.2

The recurrence rate from 1952 to 1956 for patients without attack for 2 or more years was ten times higher in the poor environmental group than among patients of a more favorable socioeconomic status (10.2 per cent to 0.7 per cent), as shown in Table VI and Fig. 6. Patients with recent activity, living under poor environmental conditions, experienced recurrences two times more frequently than those in a more favorable environment (27 per cent to 13 per cent).

TABLE VI. RECURRENCE RATES AMONG RHEUMATIC CHILDREN, AGED 4-16, 1946-51 AND 1952-56, BY ENVIRONMENTAL STATUS AND INTERVAL SINCE PREVIOUS ATTACK

PERIOD	(I AND II) GOOD TO FAIR ENVIRONMENT						(III) POOR ENVIRONMENT					
	(A) 2 YRS. OR MORE SINCE LAST ATTACK			(B) LESS THAN 2 YRS. SINCE LAST ATTACK			(A) 2 YRS. OR MORE SINCE LAST ATTACK			(B) LESS THAN 2 YRS. SINCE LAST ATTACK		
	P-YRS.	REC.	RATE (%)	P-YRS.	REC.	RATE (%)	P-YRS.	REC.	RATE (%)	P-YRS.	REC.	RATE (%)
1946–51	183.5	13	7.1	220.0	34	15.4	124	8	6.4	69.5	15	21.6
1952–56	297.0	2	0.7	155.0	20	12.9	69	7	10.1	72.0	20	27.5

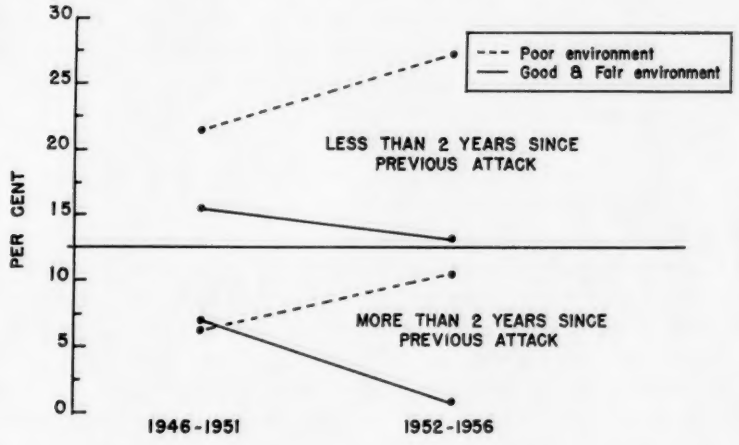

Fig. 6.—Comparison of recurrence rates during two calendar periods according to environmental status and interval since previous attack, for a total of 1,190 person-years.

It would appear that the environmental status is an influential factor in the risk of recurrences. The decline in recurrence rates coincided with the improvement in socioeconomic status, particularly during the period 1952-1956. The recurrence rates for the poorest environmental group during these latter years did not reveal the decline noted for the total clinic population.

ADDITIONAL OBSERVATIONS

During the period 1936-1956 there were 47 deaths from all causes among 782 children with 5,664 person-years of observation, between the ages of 2 and 20. Almost two-thirds (62 per cent) of these occurred in the 44 per cent of children in the poorest environment (2,231.5 person-years).

Of the deaths between 1936-1945, 58 per cent (25 of 43) were among patients of the poorest environmental group (III) who composed 50 per cent of the population under observation at that time. However in the later 11 years, 1946-1956, only 4 deaths occurred, all of which were among the children in the poorest environment who then composed only 35 per cent of the population. No deaths have occurred in the more favorable environmental groups since 1940, in 1,550.5 person-years of observation, although about 18 would have been expected if the death rate of 13 per 1,000 observed during 1936-1940 had continued to prevail.

The beginning of the decline in annual recurrence rates antedated the antimicrobial era, and the over-all decline did not appear to be sharper during 1952-1956 when antibiotics were administered to patients either during febrile illness or as continuous prophylaxis. However, the decline was greater in the better environmental groups during this period. There was no significant difference in recurrence rates between the prophylaxis group and the group treated on indications. Therefore, it would appear that adequate antibiotic therapy, if a factor, is equally effective when used for febrile respiratory infections or in continuous prophylaxis. A more comprehensive study of the effect of prophylaxis is in progress and will be reported subsequently.

COMMENT

It is apparent from the observations presented that there has been a definite decline in frequency of recurrences of the major manifestations of rheumatic fever from 1936 in our rheumatic clinic population in Greater New York City. Various possible influential factors which may have contributed to this downward trend in recurrence rates were considered. The only factor shown to have changed over the years was a progressive improvement in the socioeconomic status of the clinic population.

Of importance is the observation that there was no significant decline in the recurrence rate over the 21 years for children in the poorest environmental group. In this poorer group, from 1952 to 1956, there was a rise in the recurrence rate which approached 1936 levels and which contrasted sharply with the extremely low rates in the last 5 years among the better environmental groups. There are no comparable studies of recurrence rates among children of varying socioeconomic status. However, Wolff, in comparing mortality rates among white and nonwhite children from 1919-1921 to those in 1948, found a greater decline among white children, attributing the slower decline among nonwhite children to adverse socioeconomic conditions. Hitchens, of Cardiff, Wales, in comparing "inception rates" in the school population from 1931 to 1950, found higher rates in the predominantly working class schools compared to schools with predominantly middle class children. Collins, in a study of the incidence of rheumatic fever as recorded in the General Morbidity Surveys of Families for 1935-36, reported higher rates in families of lower economic status.

Our observations tend to support the opinion expressed by many investigators, that improvement in the general level of the care of children is a factor in the downward trend of rheumatic fever. There is no evidence from the available data of a cause-and-effect relationship. One may speculate that there is

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a greater opportunity for any of a variety of nonspecific stresses to operate among children living under most unfavorable environmental conditions.

In the present study there did not appear to be a greater over-all decline among patients after 1952, when antibiotic therapy was instituted. A preliminary analysis did not reveal a significant difference in the recurrence rates between those on continuous oral prophylaxis and patients receiving antibiotics therapeutically. Published studies on recurrence rates among patients receiving prophylaxis do not give adequate data for comparison, either as to environmental status or to interval since last attack.

These observations confirm the previous finding that the age of the patient and the interval since last attack must be taken into account when comparing recurrence rates in varying populations, particularly when evaluating therapeutic procedures. The present study further indicates that the environmental status is an additional variable factor which must be considered.

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SUMMARY AND CONCLUSION

1. Consecutive records of 782 children born after 1916 who were under continuous, uniform, medical supervision during a 40-year period at The New York Hospital Cardiac Rheumatic Clinic, were reviewed.

2. Recurrence rates of the major manifestations of rheumatic fever for ages 2-20 years were calculated for the period 1936-1956.

3. During this 21-year period, 782 children who contributed 5,664 person-years had a total of 613 recurrences, exclusive of 15 multiple recurrences within the same calendar year, giving a crude over-all rate of 10.8 per cent per year.

4. Twenty-one consecutive annual recurrence rates at ages 2-20 gave a mean rate of 9.8 per cent per year.

5. There was a statistically significant downward trend, with a slope of −0.4 per cent per year, in the annual recurrence rates from 1937-1956.

6. The mean annual recurrence rate for those with a recent attack (within 2 years) was 21.4 per 100 person-years, three times the rate of 6.0 per cent for children free from a rheumatic attack for 2 or more years. There was a significant decline in the recurrence rates in both groups over the years.

7. A comparison of age-specific recurrence rates for the periods 1916-1943, and 1944-1956, revealed lower rates at almost every age in the latter period.

8. The approximate chance of a recurrence in any one year for all children 6-13 years of age declined from 1 in 4 before 1944, to 1 in 7 between 1944 and 1956; and for ages 14-20 the chances fell from 1 in 16 to 1 in 35.

9. The general improvement in the standard of living in Greater New York City over the past two decades was reflected in the socioeconomic composition of the clinic population: (a) the relative percentage of patients in the best environmental group increased, and those in the poorest socioeconomic status decreased; (b) recurrence rates were generally lower in the more favorable environmental groups; and (c) recurrence rates for the poorest environmental group did not reveal the decline noted for the total clinic population.

10. The initial decline in recurrence rates antedated the antimicrobial era.

11. The observed decline in recurrence rates of attacks of the major manifestations of rheumatic fever coincides with the progressive improvement in socioeconomic status for patients observed in this clinic.

APPENDIX

Material and Methods.—The records analyzed consisted of the special forms designed by the New York Heart Association for use by the affiliated clinics to document the natural history of rheumatic fever.[14] Relevant information was transferred to individual McBee Keysort punch cards which were specially designed for this study.

In this study the diagnostic criteria were uniform during the 40-year period of observation. Most of the controversial aspects of rheumatic fever stem from differences in diagnostic criteria. Although the New York Heart Association (Jones criteria, modified) has been influential in categorizing the various manifestations of rheumatic fever (both major and minor), their interpretation has varied in different published reports. In this study the diagnoses of onset or recurrences of rheumatic fever are based on the presence of active carditis, usually associated with other major or minor manifestations. Arthritis or minor manifestations suggestive of rheumatic fever, in the absence of active carditis, were not accepted.

A modified life-table method was used as the basic procedure for enumerating recurrences and relating them to person-years of observation.[16] Thus, theoretically, a child developing rheumatic fever at the age of 2 years, in 1936, and followed to the age of 20 would, if he experienced no recurrences, contribute 18 person-years to the study (one year at each age, 3 to 20) before being dropped on Dec. 31, 1954 as over the age of 20.

In the previous analysis of recurrence rates in rheumatic fever[13] exact bookkeeping of dates of births, onsets, recurrences, deaths, and withdrawals, was carried out. This exact method requires extremely complicated methods of tabulation. In the present study a preliminary analysis of the data, using average dates, produced essentially the same results in the sample studied, which consisted of the most recent period where we felt the highest probability existed of distortion of rates by the assumptions made.

To simplify the preparation and tabulation of record cards and the calculation of individual rates by age and by calendar year, all patients were arbitrarily assumed to have been born on January 1 of the same calendar year in which they were actually born. Initial attacks of rheumatic fever and recurrences were assumed to begin on July 1 and to last exactly 6 months, until December 31, during which period the patient was regarded as removed from the risk of recurrence. Accordingly, the calendar year of onset was never counted as any part of a year at risk of recurrence, and one-half year (theoretically January 1 to June 31) exposure to risk was counted in any year of recurrence.

If an initial attack or a recurrence actually carried over into a second calendar year, the patient was assumed to be exposed to risk only for the latter half of the second year regardless of the actual duration of activity, on the premise that an attack carrying over into a second year would terminate half way through the year.

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If two recurrences took place in the same calendar year, the second was not counted since, according to the preceding assumptions, the first recurrence occupied the latter half of the year and the patient was therefore not exposed to risk and could not have a second recurrence. Fifteen such second recurrences actually took place and were excluded from the computations. One patient actually had three recurrences in one year (in 1942). The excluded recurrences were distributed fairly evenly over the period of observation. Since there were 613 other recurrences, the oversimplification of the dating procedure had a trivial effect on the rates.

Forty-seven deaths and 55 withdrawals were also considered to occur uniformly on July 1, giving half a year at risk of recurrence for the patient prior to death or withdrawal in the calendar year of the event.

Age Adjustment.—Crude annual recurrence rates for ages 2 to 20 were found on analysis to be misleading, due to changes during the observation period in the proportion of older patients, aged 16 to 20, among whom the lowest rates prevailed. Therefore, the individual annual rates for 1936-1956, ages 2 to 20, were age-adjusted to a "standard population" consisting of the total number of person-years in each age group for the entire 21-year period.

Age-adjusted annual rates for ages 4 to 16 were calculated but found not significantly different from the crude observed rates for this age span, and are therefore not presented. Most of the analyses, other than that of annual rates, were restricted to the patients aged 4 to 16 years in order to avoid the introduction of the additional assumptions involved in age-adjustment.

Definition of Observed and Historical Material.—Historical material included apparently reliable reports received from parents, other physicians, hospitals, or clinics, of recurrences and of years at risk after a reported initial attack of rheumatic fever. Because we suspected that the inclusion of historical data might bias the results, separate analyses were carried out for both annual rates and age-specific rates, based on "observed" material only. This consisted of person-years and of recurrences taking place *after* the first observation by the personnel of this clinic. Rheumatic activity in progress at the time of entry was also excluded.

Comparison of the rates obtained in this manner revealed no important differences in *pattern* from those rates obtained by including historical data. However, as would be expected, the rates based on only observed material are uniformly somewhat lower because of the exclusion of those attacks beginning at and before initial observation.

Of the 5,664 person-years included in the analysis, 5,489 occurred under observation. Of the 613 recurrences included in the calculations, 515 were among patients observed prior to the recurrence. Ninety-eight recurrences occurred prior to observation or were the occasion of the first observation of the patient. These were classed as historical.

During the 21 years there were 310 onsets. The rest of the 782 patients had experienced the initial attack of rheumatic fever before 1936.

Only the data for recurrences according to interval since previous attack and by economic status are based on observed material only.

Statistical Procedures.—

Trend of annual recurrence rates: To determine if the apparent downward trend over the 21 years was significant, the best-fitting straight line was fitted to the data by least squares, and the slope of this line and the SE of the slope were determined by the appropriate formulae.[18] The downward slope differed from a horizontal line by 5 times the standard error of the slope.

Interval since last attack (Table II, Fig. 2): This analysis was calculated from 1938 on, because as the total analysis arbitrarily started from 1936, 1938 was the earliest year where we had tabulated attacks 2 years previously.

The trends by individual calendar years for the recurrence rates according to the interval since last attack could not be interpreted as statistically significant because the numbers of person-years so divided were too small.

Therefore the data were grouped into the four calendar periods shown in Fig. 2. These particular periods were chosen, after examination of several alternative combinations, as those best balancing numbers of calendar years and person-years observed. Other combinations revealed similar general trends.

Straight lines fitted to the data for both groups were shown to have a downward slope significantly different from zero. The trend of those with a recent attack was −0.7 per cent per year and for the other group −0.36 per cent.

Evaluation of socioeconomic status: All patients registered in this children's cardiac clinic were interviewed by a social worker who made an initial home visit. Subsequent home visits were made over the years. Supplemental information was obtained from social agencies. All pertinent data were recorded on New York Heart Association social history forms.

For purposes of analysis, the same social worker evaluated the socioeconomic status as follows: I (good), included families having an adequate income which was utilized for good living conditions including housing, food, proper clothing, and sensible management of children's hygiene. The poorest (III) environmental group comprised families who either had inadequate income or, for social reasons, did not utilize same for proper food and shelter. The environmental group termed "fair" (II) fell in between the "poor" and "good" groups and, in the majority of these families, one or both parents made the best of fairly adverse existing conditions. The judgment of the same social worker who, over the years, had intimate contact with the families lends support to the probable validity and internal consistency of groupings made, although they were not based on numerical objective criteria.

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FAMILIAL AND EPIDEMIOLOGIC ASPECTS OF CORONARY DISEASE AND HYPERTENSION

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TO STEM the rising tide of hypertension and coronary heart disease is one of the most challenging problems in preventive medicine. Despite the fact that such cardiovascular disease causes more than half the deaths in this country today, its origin is little understood and resembles Winston Churchill's definition of Russia: "It is a riddle wrapped up in a mystery inside an enigma." It has long been thought that transitory elevation of blood pressure or excessive variability of the blood pressure were evidences of a possible prehypertensive state, but not until the studies of blood pressure in army officers by Hillman, Levy, Stroud, and White was this observation established on a sound factual basis.[1a-c] They also studied the prognostic significance of transient tachycardia and of overweight.[1d-f] Transient hypertension, transient tachycardia, or overweight, each by itself, was found to increase the probability of the later development of sustained hypertension and of disability or death from cardiovascular renal disease. In addition, it was demonstrated that the presence of *two* of these conditions was of greater importance in these respects than any one alone, while the presence of all *three* was a circumstance of major prognostic significance. Thus when transient hypertension, transient tachycardia, and overweight were all present in the same individual, the rate of subsequent sustained hypertension was twelve times as high as among those with none of these traits.

These were retrospective studies with limitations imposed by the facts available. To me it was apparent that detailed information concerning many more factors was needed before there would be a rational basis for preventive measures and that these data could be satisfactorily obtained only *before* rather than *after* degenerative processes were established. Therefore, a study of factors which may be significant precursors of hypertension or coronary heart disease was launched in 1946, under the Department of Preventive Medicine at the Johns

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Support for the long-term study has come from the following sources: Research Grant 215, the United States Public Health Service, Federal Security Agency; funds made available for research by Abbott Laboratories, Eli Lilly and Company, Lederle Laboratories Division, American Cyanamid Company, Parke, Davis and Company, and The Upjohn Company; Research Contract V1001M-2768, Veterans Administration; Research Grant H-1891, National Heart Institute; the Tobacco Industry Research Committee.

TABLE I. PARENTAL HYPERTENSION AND/OR CORONARY DISEASE AMONG 724 JOHNS HOPKINS MEDICAL STUDENTS

STUDENTS REPORTING	1948-1954 N = 353		1955-1959 N = 371		TOTAL SUBJECTS N = 724	
	NO.	%	NO.	%	NO.	%
A parent's death from these causes	27	7.6	30	8.1	57	7.9
A parent with severe disease (stroke, coronary occlusion, heart failure)	26	7.4	25	6.7	51	7.0
A parent with moderate disease (angina pectoris, enlarged heart, etc.)	16	4.5	10	2.7	26	3.6
A parent with mild hypertension	24	6.8	32	8.6	56	7.7
Total with positive parental history	93	26.3	97	26.1	190	26.2

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Hopkins School of Medicine, using the medical students as subjects.[2,3] Based on the hypothesis that essential hypertension and coronary heart disease are associated disorders in which multiple factors play a determining role, the investigation was for the purpose of seeking out factors which may be of value in the prediction and prevention of such so-called "degenerative" cardiovascular disease. These factors were thought to include constitutional differences based on genetic inheritance which may be identified before the establishment of clinical disease. Accordingly, we undertook to study the occurrence, nature, and interrelationship of a variety of genetic, physiologic, psychologic, and metabolic characteristics of young adults and by follow-up studies to determine which traits are most frequently associated with early onset of disease. The exact form of disease and age of onset in a given individual were thought to depend upon the nature and number of the factors in his own genetic inheritance in combination with the particular environmental stresses encountered as he goes through life. The possibilities opened up by such an approach were vast, and after eleven years of pursuing some of them, it may be said that we seem to be engaged in more of a Lewis and Clark expedition than an orthodox epidemiologic study!

First, I shall show some results of the family studies. With the assistance of the students themselves, we have obtained detailed information concerning the occurrence of hypertension and coronary disease, as well as diabetes and obesity, among their grandparents, aunts, uncles, and—most important of all—their parents.[4] Table I gives the spectrum of parental hypertension and coronary disease as reported by the students while in medical school. The parents were almost all between 45 and 64 years old, at a mean age of about 57 years for fathers and 53 years for mothers. The parental history is shown here for two groups of students: the findings reported for the early classes (1948-1954) have already been published; those for the classes of 1955-1959 are very similar.[3] When the two groups are combined, the spectrum provided by the parental history may be summarized as follows:

1. Among 724 subjects whose parental history is known, 190, or 26 per cent, had at least one parent with definite hypertension or coronary disease.

2. Before graduating from medical school, nearly 8 per cent of the students had lost one parent from these diseases, including sudden death.

3. Another 7 per cent have a parent living with severe disease, as indicated by a history of coronary occlusion, stroke, or cardiorenal failure.

4. Eleven per cent of the students have a parent living with moderate or mild disease, including angina pectoris and the less severe forms of hypertension.

5. In addition to those with positive parental history, approximately 10 per cent of subjects have a parent with questionable hypertension or coronary disease, while a similar number have an obese or diabetic parent.

6. A few subjects cannot determine their parental history accurately because of divorce, early death from other causes, and so on.

7. No more than half of the students in medical school can definitely state that both parents are thus far free from these four closely related disorders.

TABLE II. 57 FATAL CASES OF HYPERTENSION AND/OR CORONARY DISEASE AMONG PARENTS OF 724 JOHNS HOPKINS MEDICAL STUDENTS

TERMINAL CONDITION	PARENT AFFECTED	N	AGE AT DEATH				
			30-39	40-49	50-59	60-69	70-79
Coronary Occlusion	Fathers	34	2	7	16	8	1
	Mothers	3	2	0	0	1	0
Stroke	Fathers	8	0	1	2	3	2
	Mothers	5	0	0	5	0	0
Cardiorenal Failure	Fathers	5	0	3	1	1	0
	Mothers	2	0	1	1	0	0
Total	Fathers	47	2	11	19	12	3
	Mothers	10	2	1	6	1	0
	Parents	57	4	12	25	13	3

Analysis of the 57 parental deaths shows that coronary occlusion, including sudden death, accounted for about two-thirds of the fatalities (Table II). Stroke caused nearly one quarter, while cardiac or renal failure accounted for the remainder. Nearly five times as many fathers died as mothers. Thirteen of the 34 fathers who died of coronary occlusion had had one or more previous attacks; half of those who died a coronary death in their 50's had had their first heart attacks in their 40's. Not only did the male sex predominate in regard to coronary deaths, but more fathers died from stroke as well. Before the age of 60, 32 of the 724 fathers and 9 of the 724 mothers had died from cardiovascular disease of these types, an incidence of 44.2 per 1,000 and 12.4 per 1,000, respectively. These mortality rates are by no means final ones, since the majority of parents were considerably under 60 when the data were obtained. If, in the coming years, the prevalence of these disorders remains the same, well over 5 per cent of male medical students may be expected to die of coronary disease or some form of hypertension when in their 40's or 50's.

We have reported the prevalence of hypertension and coronary disease, both separately and combined, in two successive generations.[4] In this portion of the study, the grandparents of the students were called the *parental generation* while the students' parents, aunts, and uncles comprising the second generation were called the *offspring*. Three types of parental matings were considered: Type I where both marital partners were affected, Type II where one partner was affected, and Type III where neither partner was affected. In every case, the proportion of affected offspring was greatest where both parents suffered from some form of these disorders and least where neither parent was affected. In the case of the combined disorders, for example, the incidences of disease in the offspring of the three types of mating were as follows: Type I, 22 per cent; Type II, 12 per cent; and Type III, 8 per cent. Thus, 2.7 times as many offspring of Type I matings were affected as offspring of Type III matings.[5] The gradation in disorder rates among the offspring of the three types of mating is consistent with the Mendelian law of segregation. More evidence is needed, however, before the genetic basis for these disorders is fully established.

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The various patterns of parental disease provide a basis for classifying subjects so that the frequency of a trait among students with adverse inheritance and among those with normal parents may be compared. For example, a study was made of the differences to be found between the offspring of hypertensive parents and of normal parents in regard to a number of characteristics related to blood pressure, heart rate, circulatory hyperreactivity, and overweight.[6] In general, higher, more labile blood pressure and heart rate and overweight were more frequent among students with a positive parental history of hypertension. Although the difference between the two groups as to incidence of single traits was often not great, about 40 per cent of the offspring of hypertensive parents had *multiple* positive traits, two and a half times as many as were found among the offspring of normal parents. Students with hypertensive parents were also more reactive to cigarette smoking than were subjects with normal parents, while those with coronary parents were less reactive. The effect of smoking a single cigarette on systolic pressure, diastolic pressure, pulse pressure, heart rate, stroke volume, and cardiac output was measured on a table ballistocardiograph.[7] The percentage increase or decrease from the control value produced by smoking was determined for groups of subjects which differ as to inheritance. The offspring of hypertensive parents were characterized by an exaggerated increase in cardiac output amounting to 992 c.c. per minute, or 13 per cent above control values. They also had the greatest average rise of systolic and diastolic pressure and heart rate, and stroke volume did not decrease. On the other hand, those with coronary parents were characterized by the most marked diminution in stroke volume of any group, so that the increase in cardiac output after smoking was much less—only 117 c.c. per minute, or 2 per cent, compared with 399 c.c. (5 per cent) for subjects with normal parents. These differences were statistically significant and strongly suggest that the circulatory response to smoking in healthy young adults depends in part upon the physiologic heritage of the individual.

Turning to the coronary end of the spectrum, we have found that hypercholesteremia, or cholesterol levels of 300 mg. per 100 c.c. or more on at least one

occasion, is much more frequent among the offspring of parents with coronary disease than among those with normal parents.[8] In the entire group of hypercholesteremic students, 32 per cent had a parent with coronary disease in contrast to 12 per cent of those with normal cholesterol values—a highly significant statistical difference. It appears, then, that positive parental history and positive individual traits often go hand in hand.

We have recently described a new four-way grouping of healthy subjects according to *both* parental history and individual characteristics.[5] This classification is proposed as the basis for selection of highly susceptible individuals in testing preventive measures against hypertension and coronary heart disease. The four-way grouping is shown in Table III. "Group I, where both the parental and individual factors are positive, stands in sharp contrast to Group IV, where both these significant factors are negative. These two groups are expected to produce the highest and lowest attack rates respectively. In Group II, where familial and individual factors are discordant, the parent may develop disease later, thus transforming a Group II into a Group I subject, or the traits may be inherited as recessives, or the traits may be due to environmental factors. Group III, also discordant, includes those who have escaped an adverse inheritance, those who are healthy carriers of recessive traits, and those who may develop positive traits at a later time. Group I provides subjects most suitable for tests of preventive measures."

TABLE III. FOUR-WAY GROUPING OF HEALTHY SUBJECTS AS A BASIS FOR PREVENTIVE MEASURES AGAINST HYPERTENSION (H+) AND/OR CORONARY HEART DISEASE (C+)

GROUP	SIGNIFICANT FACTORS		PROBABILITY OF DEVELOPING DISEASE
	PARENTAL H+/C+	INDIVIDUAL TRAITS	
I	+	+	High
II	−	+	Fairly high
III	+	−	Doubtful
IV	−	−	Low

From Ann. Int. Med. 47:389, 1957.

Table IV gives some illustrative examples of subjects from the four groups. "The positive traits appear in varying combinations in different individuals. The likelihood that a single positive characteristic may be fortuitous or have little meaning in terms of life expectancy has led us to place persons showing such an isolated trait in the 'negative trait' groups. The relative size of each group depends upon such determinants as the age of parents and the arbitrary limits chosen in defining as 'positive' and 'negative' traits which actually vary continuously. Using definitions consistent with those previously published, we have found, after reviewing the findings on 534 students in seven consecutive classes, that about one-sixth of the subjects fall in Group I, a similar number in Group

II, and a few less in Group III. Nearly one-third fall in Group IV; the remainder cannot be definitely classified, chiefly because of uncertainty in regard to parental histories."

TABLE IV.

SUBJECT NO.	GROUP	GENETIC FACTOR	INDIVIDUAL CHARACTERISTICS				
		PARENTAL H+/C+	HIGHER CHOLESTEROL LEVELS	NON-ECTOMORPHY (OVERWEIGHT AND/OR MESOMORPHY)	HIGHER B.P. LEVELS	HIGHER HEART RATE	HYPER-REACTIVITY TO COLD AND/OR EXERCISE
51141	I	+	−	+	+	−	+
53101		+	+	+	+	+	+
54168		+	+	+	−	+	+
56106		+	+	−	+	+	−
51140	II	−	−	+	−	−	+
53108		−	−	+	+	+	+
55235		−	+	−	−	+	+
57134		−	+	−	−	+	−
51123	III	+	−	−	−	−	−
52119		+	−	−	−	+	−
55158		+	−	+	−	−	−
57102		+	−	−	−	−	−
51122	IV	−	−	−	+	−	−
52113		−	−	−	−	−	−
53105		−	−	−	−	−	−
57103		−	+	−	−	−	−

From Ann. Int. Med. 47:389, 1957.

TABLE V. THE RATIO OF SMOKERS TO NONSMOKERS AMONG MEDICAL STUDENTS GROUPED ACCORDING TO SUSCEPTIBILITY TO HYPERTENSION AND/OR CORONARY DISEASE

FOUR-WAY GROUP	N	SUSCEPTIBILITY TO H+/C+	SMOKERS (%)	NONSMOKERS (%)	RATIO
I	74	High	60.8	39.2	1.6
II and III	137	Intermediate	50.4	49.6	1.0
IV	129	Low	41.9	58.1	0.7

Such a classification may also contribute to the further understanding of the susceptible individual. For instance, because of current concern over a possible link between smoking and coronary disease, we have looked into the smoking habits of the students classified according to the four-way grouping. Whereas 61 per cent of those in Group I—the highly susceptible group—were smokers and 39 per cent were nonsmokers, just the reverse was true for those of low susceptibility in Group IV (Table V). In Groups II and III there were about even numbers of smokers and nonsmokers. The actual number of smokers expected and observed in each of the four groups is shown in Table VI. When Groups II and III are eliminated and X^2 with one degree of freedom is calculated for smokers

and nonsmokers in Groups I and IV only, the difference is significant at the 1 per cent level. In other words, a parallelism seems to exist between the degree of susceptibility to future cardiovascular disease and the habit of smoking, the highest proportion of smokers occurring in the group with highest susceptibility and the lowest proportion of smokers in the least susceptible group of students.

TABLE VI. THE PROPORTION OF SMOKERS AMONG 340 HEALTHY SUBJECTS GROUPED ACCORDING TO PROBABLE SUSCEPTIBILITY TO FUTURE HYPERTENSION AND/OR CORONARY HEART DISEASE (H+/C+)

FOUR-WAY GROUP	N	SUSCEPTIBILITY TO H+/C+	SMOKERS (N = 168)		NONSMOKERS (N = 172)	
			OBS.	EXP.	OBS.	EXP.
I	74	High	45*	36.6	29*	37.4
II	72	Intermediate	35	35.6	37	36.4
III	65	Intermediate	34	32.1	31	32.9
IV	129	Low	54*	63.6	75*	65.4

*$X_1^2 = 6.8$ $p < 0.01$

TABLE VII.

SMOKING HABITS OF STUDENTS	PARENTAL HYPERTENSION			
	PRESENT OR QUESTIONABLE		ABSENT	
	OBS.	EXP.	OBS.	EXP.
Nonsmokers	80	93.3	196	182.7
Regular Smokers	113	99.7	182	195.3

$X_1^2 = 5.54$ $0.025 > p > 0.01$

We then studied the relationship of smoking to the various components of the four-way classification to see whether smoking is associated with positive parental history, with positive individual traits, or both.[9] The main findings of this study, soon to be published, can be mentioned only briefly here. The incidence of parental hypertension and coronary disease was higher among subjects who were regular smokers than among subjects who were nonsmokers or occasional smokers. The difference was highly significant ($p < .025$) when subjects with a parental history of definite or questionable hypertension were compared with subjects whose parents were free from that disorder (Table VII). When subjects with and without a history of parental coronary heart disease were compared, the difference was not significant, although it approached the

5 per cent level (Table VIII). It should be recalled here that the mean age of these parents was about 55 years. Accordingly, a large proportion of the fathers and mothers destined to develop hypertension of the diastolic type have already done so whereas many of the fathers and almost all of the mothers who will ultimately have coronary heart disease are still in good health. There were more nonsmokers and fewer regular smokers than expected among the subjects whose parents are both entirely free from hypertension and coronary heart disease as compared with all other subjects, including those whose parents have various forms of those disorders (Table IX). The difference was significant at the 2.5 per cent level.

TABLE VIII.

SMOKING HABITS OF STUDENTS	PARENTAL CORONARY HEART DISEASE			
	PRESENT OR QUESTIONABLE		ABSENT	
	OBS.	EXP.	OBS.	EXP.
Nonsmokers	65	74.6	214	204.4
Regular Smokers	88	78.4	205	214.6

$X_1^2 = 3.29 \quad 0.10 > p > 0.05$

TABLE IX.

SMOKING HABITS OF STUDENTS	PARENTAL HISTORY			
	BOTH PARENTS FREE FROM *HYPERTENSION* AND CORONARY DISEASE		ONE OR BOTH PARENTS WITH POSITIVE, QUESTIONABLE, OR UNKNOWN HISTORY	
	OBS.	EXP.	OBS.	EXP.
Nonsmokers	160	145.3	147	161.7
Regular Smokers	140	154.7	187	172.3

$X_1^2 = 5.47 \quad 0.025 > p > 0.010$

Of the individual factors studied, one of the most significant differences between smokers and nonsmokers was found in respect to the serum cholesterol level. This fact is a new finding of considerable potential interest. In Table X, we see that at the three lower cholesterol levels (under 250 mg. per 100 c.c.), smokers are in the minority, whereas at higher levels (of 250 mg. per cent or

above), the smokers predominate. This is especially true for the 48 hypercholesteremic subjects, 62.5 per cent of whom were smokers. Using 250 mg. per 100 c.c. as the cutting point for "lower" versus "higher" cholesterol levels, we have compared the expected and observed number of smokers and nonsmokers in this fourfold table and find that the association between the habit of smoking and higher cholesterol levels is significant at the 2 per cent level (Table XI). Our data do not indicate whether smoking increases the level of cholesterol or whether students with higher cholesterol levels are more likely to smoke. However, the fact that the parental histories of smokers and nonsmokers are not just alike leaves open the possibility that differences in individual traits may be genetic in origin, at least in part.

TABLE X. PERCENTAGE OF SMOKERS AND NONSMOKERS AT EACH CHOLESTEROL LEVEL

HIGHEST CHOLESTEROL LEVEL (MG. %)	SMOKERS (N = 264) (%)	NONSMOKERS (N = 257) (%)
< 200	44.4	55.6
200-224	47.5	52.5
225-249	47.7	52.3
250-274	55.3	44.7
275-299	55.0	45.0
300+	62.5	37.5

TABLE XI. COMPARISON OF SERUM CHOLESTEROL LEVELS IN SMOKERS AND NONSMOKERS

HIGHEST CHOLESTEROL LEVEL (MG. %)	SMOKERS (N = 264)		NONSMOKERS (N = 257)	
	OBS.	EXP.	OBS.	EXP.
Under 250	149	161.6	170	157.4
250 or above	115	102.4	87	99.6

$X_1^2 = 5.2$ $p = 0.02$

The ultimate significance of our own observations in terms of prevalence of cardiovascular disease among the various groups of subjects studied must await follow-up studies over the years to come. However, reports of other prospective studies on the association of multiple factors with later disease, using older subjects observed for several years, are now beginning to appear.[10] This year the Framingham Study group published findings based on the first 4-year follow-up of their cardiovascular survey of a cross section of the Framingham population who were aged 30 to 59 years on entering the study.[10a] They found significant statistical associations between high blood pressure,* excessive weight and/or high cholesterol levels, and an increased incidence of subsequent coronary heart

*Whether definite or borderline, and whether or not associated with hypertensive heart disease.

disease. Most important, the use of three factors in combination—blood pressure, relative weight, and serum cholesterol—permitted the separation of their subjects into groups with highly divergent risks of coronary disease. The incidence of new disease was 143 per 1,000 in men with two or more positive traits as opposed to 10 per 1,000 for those without any of the three traits. At the same time, groups from Albany and Los Angeles reported on cardiovascular population studies with follow-up information for periods of less than three years.[10b,10c] The Albany group found nearly six times as much coronary disease appearing in those with initial cholesterol levels of 275 mg. per 100 c.c. or over, as opposed to those with initial levels of less than 200 mg. per 100 c.c. Also, those with gross overweight, well-marked weight gain from the age of 25 on, or abnormal electrocardiograms developed coronary disease two or three times as often as those who did not. The interaction of these factors was not analyzed. The Los Angeles group found a higher incidence of coronary disease among men 40 to 54 years old with higher relative weight or higher systolic pressure or higher diastolic pressure to begin with than among men of similar age without these attributes, but the positive associations no longer held in those over the age of 55.

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Nothing was said in two of these studies about the significance of a positive family history of hypertension or coronary disease. In the Albany report it was stated that "a family history of vascular disease . . . failed to show significant associations with ischemic heart disease," but the particulars were not given. However, in a recent analysis of the prognostic value of life insurance mortality investigations, Bolt and Lew brought forward the importance of a family history of cardiovascular-renal disease.[11] For the first time, studies were made on a group of 11,600 insurance applicants who reported two or more cases of cardiovascular-renal disease occurring in persons under the age of 60 in the immediate family as compared with standard risks. Over a 15-year period, those applicants, aged 30 through 64, whose family history was marked by early cardiovascular disease, suffered from 1.4 times as many deaths as did the standard risks. The group with positive history "was characterized by an excess mortality from cardiovascular-renal conditions; in the aggregate the death rate from these causes was nearly double that for standard risks and accounted for most of the excess mortality." A supplementary study showed: "among insured persons who, in addition to having reported a family history of early cardiovascular-renal disease, either were slightly overweight or had a slight elevation in blood pressure, deaths were 1.7 times those among standard risks, whereas, among those reporting a family history of early cardiovascular-renal disease but free from these impairments, deaths were only 1.25 times those among standard risks. The difference between 1.7 and 1.25 may seem small, but statistically it is significant . . . . Insofar as these figures go, they indicate that a combination of a family history of early cardiovascular disease together with conditions associated with cardiovascular disease, such as excessive weight or hypertension, is of much greater consequence than these associated conditions alone." Cholesterol levels were not included in their studies.

With all these facts before us, it is evident that the long first step has been taken. In general, we now know who the highly susceptible candidates for coro-

nary disease and hypertension are—namely, those with a positive heritage and multiple positive individual traits. While not all such Group I individuals will develop disease in middle life, a substantial proportion will. Now is the time to start the actual task of prevention. By selecting these susceptible subjects on a wide scale and dividing them into test and control groups, the way is clear to begin the appraisal of various measures calculated to postpone and ultimately to prevent these diseases.

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THE RESULTS OF TREATMENT IN 1,086 GENERAL PARALYTICS THE MAJORITY OF WHOM WERE FOLLOWED FOR MORE THAN FIVE YEARS

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I AM greatly honored to have been invited to address you as the spokesman for a group of clinics which includes the Bellevue, Boston Psychopathic, St. Elizabeths, Grady Memorial (Emory University), Johns Hopkins, New York, University of Michigan, and University of Pennsylvania Hospitals. The records of 1,086 paretic patients from all these institutions were pooled and analyzed statistically with the assistance of Mrs. Geraldine A. Gleeson and Dr. John C. Cutler of the United States Public Health Service. My chief, Joseph Earle Moore, gave invaluable constructive criticism and advice.

The present study is an evaluation of the therapeutic efficacy of penicillin in 1,086 patients with general paralysis. The possible additive effects of fever therapy are also considered. No untreated control group is available, but the end point in untreated general paralysis, as evidenced by the literature before the introduction of malaria therapy in 1917, is death, usually within a period of 4 years from detection.

To provide for the uniform coding of records at the various cooperating institutions, work sheets of the multiple choice variety were drawn up, and the results transferred to punched cards. The fixed point of reference with respect to time was the so-called "study treatment" date. This was the treatment episode which placed the patient in the study group, whether or not previous treatment had been given elsewhere.

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Patients were observed at 3, 6, and 12 months after study treatment, and yearly thereafter. At each observation a worksheet was filled out with a comparison of the status at that time with the status preceding study treatment.

Of the 1,086 patients, 629 were treated with penicillin alone, and 457 with penicillin plus fever therapy, usually induced tertian malaria. The period of observation after treatment is shown in Table I. The fact that over 90 per cent of these patients were followed for 1 year or more and 60 per cent for 5 years or more lends a certain validity to the conclusions of the present study.

TABLE I. POSTTREATMENT OBSERVATION: 1,086 PARETICS

1 year or more	92%
3 years or more	79%
5 years or more	60%
7 years or more	34%

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Information as to previous treatment was unavailable in 20 per cent of cases Almost 40 per cent of those for whom such information was available had been entirely untreated at any time. Only 5 per cent of patients had received any penicillin. Consideration of the stage of infection when treatment was first given revealed that only 1 out of 10 patients had received any treatment for early syphilis and in no case had therapy included penicillin. A recently published study by the same cooperative group of 765 patients with asymptomatic neurosyphilis followed in most cases more than 5 years after penicillin treatment showed that paresis did not develop under these circumstances within the observed post-treatment period.

The duration of syphilitic infection could not be determined in half of these patients, and in the remainder had a spread, as roughly estimated from the histories provided by psychotic patients, of from 2 to more than 30 years, with the majority falling in the period of 10 to 24 years.

In the present large group of patients, paresis was seen approximately three times as frequently in males as in females, and over twice as frequently in whites as in Negroes. Eighty-five per cent of the patients were in the age group of 30 to 59 years.

The spinal fluid complement fixation test was positive at the time of treatment in all of the 327 previously untreated patients, 85 per cent of whom showed 5 or more cells. In 92 per cent of the same untreated group the blood S.T.S. at the time of treatment was positive.

As shown in Table II, the simple dementing type of psychosis was more frequent than all the others combined.

In Table III is shown the percentage distribution with respect to duration of paretic symptoms at the time of treatment. In paretics the great difficulty of obtaining a reliable history in this regard, even from the patient's family and associates, is well known. A not inconsiderable percentage of the present group failed to give sufficient information for even an estimation of the onset. Ideally, paresis should be promptly diagnosed and as promptly treated. The present

group represents, by and large, a far different situation with only 16 per cent of the patients entering the study with symptoms of 3 months' duration or less. The benefit of treatment reported here may thus be considered to be minimal.

TABLE II. TYPE OF PSYCHOSIS

Simple dementing	59.8%
Manic, expansive	18.1%
Depressed	5.8%
Paranoid	6.4%
Somatic signs only	3.2%
Unclassified	6.7%

TABLE III. DURATION OF PARETIC SYMPTOMS

MONTHS	PER CENT
0–3	15.9
4–6	10.8
7–12	17.9
13–36	19.6
37+	15.3
Unknown	20.5

TABLE IV. CLINICAL SEVERITY OF INVOLVEMENT

Severe	56.3%
Moderate	21.5%
Mild	22.2%

In order to provide some basis for prognosis and for comparison of other variables, an attempt was made to estimate the "severity" of clinical paretic involvement at the time of treatment. Arbitrarily the following criteria were considered to be indicative of advanced disease (referred to as group I symptoms): psychotic on simple observation, delusions, disorientation, incontinence, untidy dress, illogical conversation, and inability to perform simple acts of personal toilet. Symptoms considered to indicate less advanced paretic involvement (group II symptoms) included impairment of retention, memory, information, calculation, judgment, insight, speech, handwriting, and the presence of tremors.

Patients who had two or more group I symptoms were classified as having "severe" paresis. Patients who had only one or none of the group I symptoms, but five or more of the group II symptoms, were classified as having "moderate" paretic involvement. Patients who had only one or none of the group I symptoms and less than five of the group II symptoms were classified as having "mild" paretic involvement. The percentage distribution of cases with respect to this classification is shown in Table IV. There are several reasons for believing,

despite its arbitrary nature, that the classification used is a valid one. It correlates well with the source of cases, as 375 of the 611 cases classified as severe come from the only two psychiatric hospitals among the eight cooperating institutions (St. Elizabeths and the Boston Psychopathic). It also correlates well with the pragmatic factor of ability to work, since only 3 per cent of paretics classified by our criteria as "severe" were able to work at the time of treatment contrasted with 33 per cent of those classified as "moderate" and 53 per cent of those classified as "mild."

Severity of clinical psychosis did not correlate well with estimated duration of paretic symptoms. It is felt that this lack of correlation is more apparent than real and is due at least in part to the unreliability of such historical data concerning duration of symptoms as is obtainable from psychotic patients and/or their frequently unintelligent or unobservant relatives and associates.

I omit details as to the type and amount of penicillin given to these patients except to say that most of them were treated at a time when aqueous penicillin was in vogue. Almost all of them received over 2.4 million units, and a bit over half of them received more than 6 million units. There was a definite tendency to treat clinically "severe" paretics with larger dosage. There was also a similar tendency to add fever therapy to penicillin more frequently in the "severe" paretics. It is of interest that the trend in recent years in the United States has been toward utilization of penicillin alone.

Herxheimer reactions, both clinical and febrile, occurred significantly more frequently after treatment in patients with pleocytosis (of 11 or more cells) than in those without pleocytosis in the spinal fluid. Among the 44 clinical Herxheimer reactions, exacerbation of the psychosis or the development of convulsive seizures were the major problems, occurring in 24 and 6 patients, respectively. One patient died in status epilepticus.

Broadly considered, the results of treatment of paretics may be evaluated from two points of view—the physical and the psychiatric outcome. Utilizing a modified life table technique, all patients were carried through to latest observation, re-treatment, or death. The cumulative probability of death was thus determined. Death was further categorized as to cause, i.e., neurosyphilis or other reasons.

The survivors were then further considered in relation to pretreatment status. In general, two measurements of psychiatric outcome have been utilized. (1) Clinical status of the paretic psychosis after treatment in relation to pretreatment status. In this determination the judgment of the clinician was paramount. The possible categorizations were (a) remission—significantly improved, (b) unchanged, and (c) progression. (2) Work status after treatment in relation to pretreatment work status—a pragmatic yardstick of evaluation largely independent of the vagaries of individual clinical judgment, but subject to a variety of imponderable general extraneous influences such as the business cycle, availability of vocational rehabilitation, and of suitable work, etc. The possible categorizations were (a) able to work, (b) unable to work but not in a mental institution, and (c) in a mental institution. Cases in which inability to work was for reasons other than general paralysis were accounted for.

In Fig. 1 is shown the cumulative probability of death among 1,086 paretics after treatment with penicillin. The lowermost curve shows the cumulative probability of death from paresis itself. This is only 4 per cent at 1 year, 5 per cent at 2 years, 6 per cent at 4 years, 8 per cent at 6 years, 9 per cent at 8 and 10 years. The second curve, which shows the probability of death from all forms of syphilis, is only slightly higher. The next curve, which shows the probability of death from causes other than syphilis, clearly indicates that even among paretics (after penicillin treatment, of course) the probability of death from syphilis is significantly less than the probability of death from extraneous causes, a startling finding in view of the formerly dread nature of general paralysis.

The top curve shows the probability of death from all causes, syphilis included. This is 8 per cent at 1 year, 12 per cent at 2 years, 17 per cent at 4 years, 23 per cent at 6 years, 28 per cent at 8 years, and 31 per cent at 10 years.

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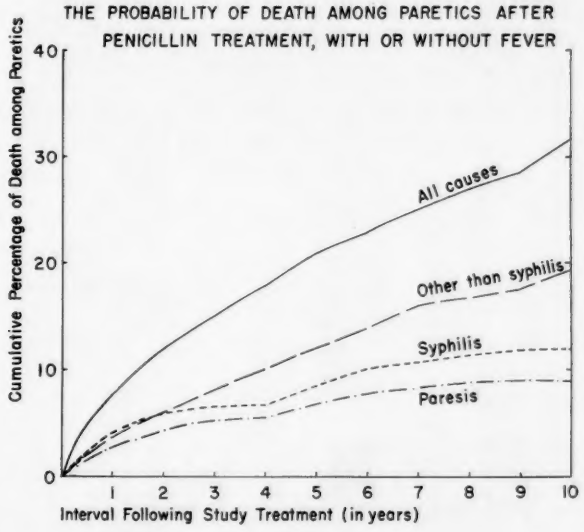

Fig. 1.

Not shown in graphic form are comparable probabilities of death for patients who received only one course of treatment since these probabilities are identical with those shown for the group as a whole. This essential identity of probability of death among those who received one and those who received more than one course of treatment is strong evidence against the necessity for routinely repeated courses of penicillin in the treatment of general paralysis.

As a matter of fact, the total role of penicillin-treated general paralysis as a cause of death is not accurately depicted by any of the curves of Fig. 1, for in addition to deaths due to neurosyphilis and other forms of syphilis, there is an excess mortality due to other diseases among penicillin-treated paretics as compared with the population at large. This excess mortality is doubtless due to

increased susceptibility as the result of varying degrees of debilitation. Somewhere between the curves depicting the probability of death due to syphilis and the probability of death due to all causes lies the true cost of paresis in terms of death. The difference in death rates between penicillin-treated general paralytics and a similar age, race, and sex group of nonsyphilitics has been estimated by computing specific age, race, sex, and total death rates in our study population—that is the number of deaths per one thousand person years of observation, and applying them to the 1950 United States population to secure a composite rate adjusted for age, race, and sex. The actual death rate for causes other than syphilis occurring in the United States, in 1950, was compared with the adjusted rate for our study group. The death rate per one thousand per annum was 10.8 for the population as a whole, and 37.7 for the penicillin-treated paretic group. It may thus be concluded that the paretic, even though treated with the best available methods, has nearly four times the death rate of his or her nonsyphilitic age, race, and sex counterpart. The best treatment of paresis remains its prevention by the prompt detection and adequate treatment of early syphilis or asymptomatic neurosyphilis.

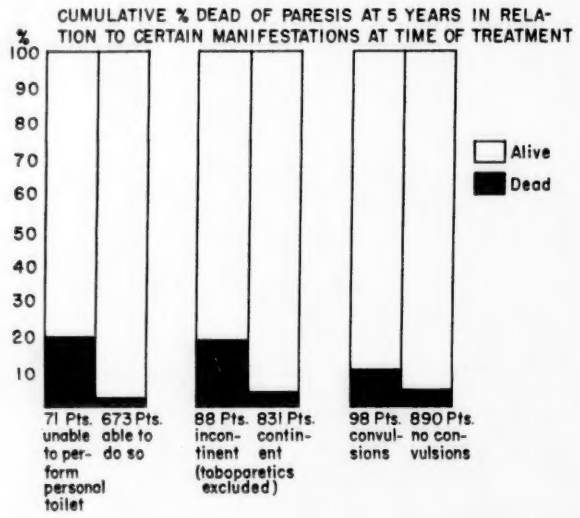

Fig. 2.

As shown in Fig. 2, the presence of certain symptoms at the time of treatment markedly influenced the cumulative per cent of patients dead of paresis at 5 years after treatment. At that time 19 per cent of paretics unable to perform simple acts of personal toilet at time of treatment were dead of paresis as compared with only 2 per cent of patients able to do so. Similarly the presence of incontinence or of convulsions afforded a less favorable prognosis.

As shown in Fig. 3 the cumulative probability of death from paresis at 5 years after treatment was 10 per cent for patients with severe psychosis when

treated, and zero for patients with moderate or mild psychosis. The cumulative probability of death from causes other than paresis was essentially identical for all three groups.

These data afford further confirmation of the classification of paresis into mild, moderate, and severe, based upon symptoms at the time of treatment. Indeed, it may be stated that the performance of a skilled neuropsychiatric examination at the time of treatment affords the clinician definite prognostic data to a certain extent as to life itself.

In Fig. 4 is shown the clinical status at 7 years after treatment in relation to "severity" of paretic psychosis. In this and subsequent figures, the number of patients followed for the full time interval stated in the chart is shown. Fig. 4 illustrates two important points; first, in mild or early cases better than 80 per cent can be rehabilitated and remain so for at least 7 years; and second, the apparent severity (as we have classified it) of the paretic psychosis at the time of treatment would appear to be of considerable prognostic import.

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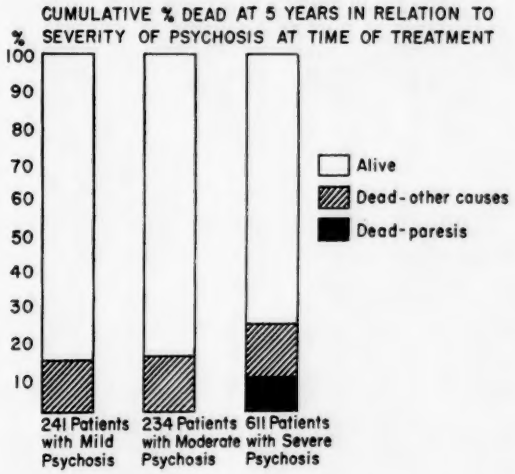

Fig. 3.

In Fig. 5 the per cent of patients in a psychiatric institution 7 years after treatment according to severity of psychosis is shown and compared with pretreatment status. Five times as many patients with apparently severe psychosis at time of treatment were in a psychiatric institution 7 years later as compared with patients originally classified as having moderate or mild psychosis. In all groups results were excellent. Progression of psychosis and death due to general paralysis occurred practically altogether in the severe group.

In Fig. 6 is shown the per cent of patients able to work 6 years after treatment in relation to work status at time of treatment. It illustrates the considerable prognostic importance of ability to work at the time of treatment but also shows

that with penicillin therapy one out of three of the least favorable group (institutionalized paretics) can be rehabilitated for some form of work. Of perhaps equal significance is the length of time which has elapsed since the patient has

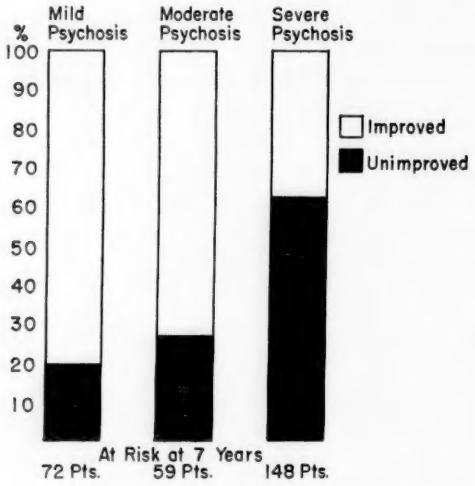

Fig. 4.—Clinical status at 7 years after treatment.

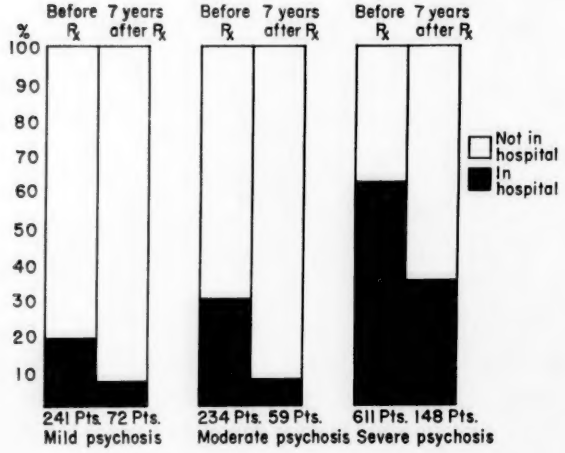

Fig. 5.—Per cent in psychiatric institution 7 years after treatment in relation to per cent institutionalized at time of treatment.

been able to work at his usual occupational level at the time of treatment, because ability to work 4 years after treatment was inversely proportional and psychiatric institutionalization directly proportional to the length of time decreased work capacity had existed at the time of treatment.

Due to the small number of cases available after subcategorization, study of ability to work after treatment at the same occupation as before treatment was not feasible. However, among 118 skilled workers and 215 unskilled workers institutionalized at time of treatment, ability to work at some socioeconomic level 5 years after treatment was not significantly different. The clinician's evaluation of the severity of the pre-treatment paretic psychosis correlated well with ability to work 5 years after treatment, as only approximately one out of three severe cases were working at any level 5 years after treatment in comparison with over 80 per cent of moderate cases and over 90 per cent of mild cases.

In Fig. 7 is shown the per cent of patients improved 5 years after treatment in relation to pre-treatment spinal fluid cell count. The higher the pre-treatment spinal fluid cell count, the greater is the percentage of clinical improvement 5 years after treatment. Progression rates and death due to neurosyphilis were, however, slightly higher in patients with pre-treatment spinal fluid pleocytosis.

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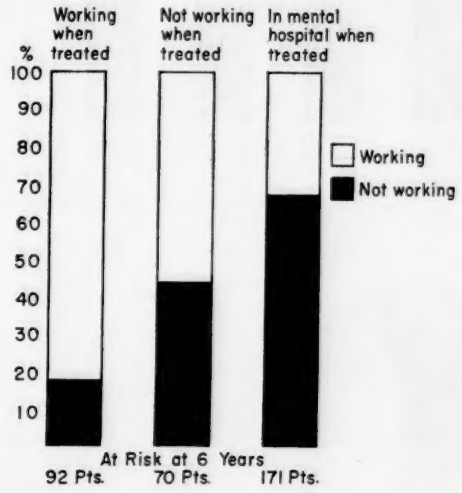

Fig. 6.—Per cent able to work 6 years after treatment.

An elevated pre-treatment spinal fluid cell count indicates an active inflammatory process more susceptible of improvement by treatment but at the same time in some cases leaving behind sufficient brain damage to nullify any real clinical effect. Patients with low cell counts (an inactive fluid), on the other hand, have a relatively static process, less susceptible of improvement by treatment, but at the same time less likely to result in clinical progression. The correlation is definite enough to be of some prognostic value but not sufficiently great to permit withholding adequate treatment from any patient with general paralysis who has not previously had treatment known to have been adequate.

Pre-treatment spinal fluid protein levels tended to show the same general relationship to clinical outcome as did cell counts, but the correlation was less definite.

In Fig. 8 is shown post-treatment cell count at 1, 3, and 5 years in relation to pre-treatment cell count. These findings are essentially similar to those previously reported in asymptomatic neurosyphilis treated with penicillin. Elevated cell counts of 11 or more had almost entirely disappeared by the end of

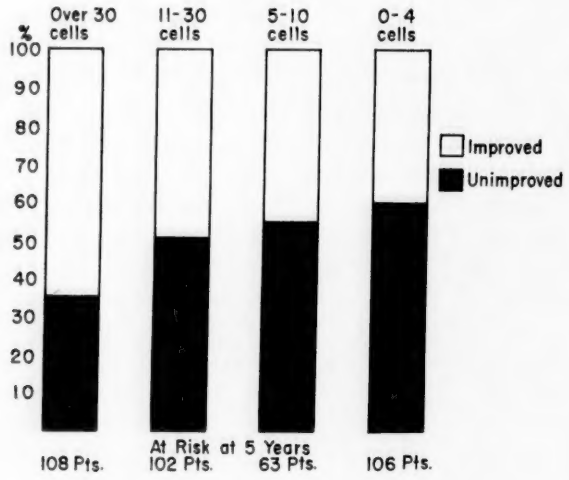

Fig. 7.—Per cent improved 5 years after treatment in relation to pretreatment cell count.

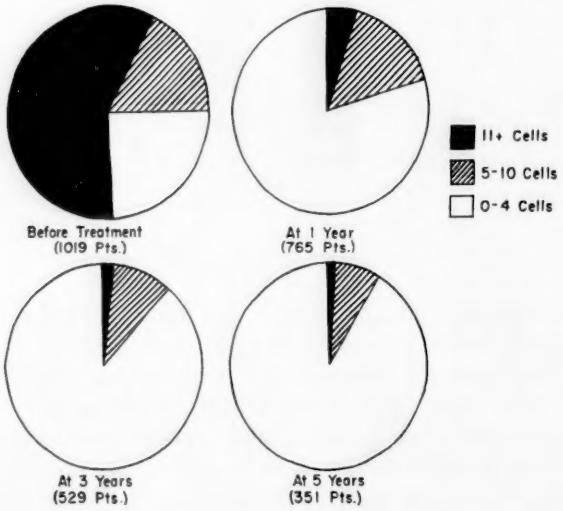

Fig. 8.—Post-treatment cell count in relation to pretreatment cell count.

the first post-treatment year. In contrast as shown in Fig. 9, elevated protein levels of 51 mg. per cent or more persisted in 10 per cent of patients at 5 years after treatment.

Since persistently abnormal cell counts of 11 or more cells were not encountered with any frequency after the treatment of paresis with penicillin, they could not be correlated with clinical outcome. Borderline cell counts of 5 to 10 were observed in a significant number of patients 3 years after treatment, at which time clinical progression was recorded in 18 per cent of this group as compared with only 6 per cent of the group with 0 to 4 cells. Although abnormal and borderline protein levels, as shown, persisted with much greater frequency than did elevated or borderline cell counts, post-treatment protein levels could not be correlated with clinical outcome.

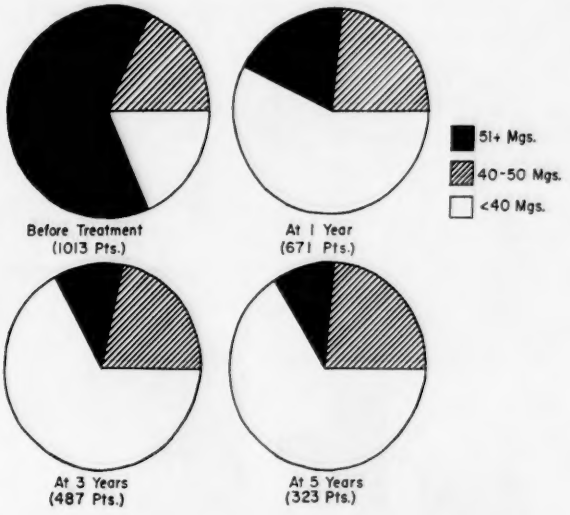

Fig. 9.—Post-treatment protein in relation to pretreatment protein.

Let us turn now to a consideration of outcome in relation to treatment received. Outcome was significantly affected by treatment given prior to entry into the study. The effect of previous penicillin therapy could not be evaluated because only 56 patients were known to have received this drug previously. At 6 years after study treatment there was a significant difference in outcome between the 327 previously untreated patients and the 483 patients previously treated with therapy other than penicillin. Improvement occurred in only 42 per cent of previously untreated patients, as contrasted with 58 per cent of previously treated patients. Differences of like degree were found with respect to ability to work and psychiatric institutionalization at 5 years after treatment.

In view of the large percentage of previously treated patients and of the demonstrably favorable effect of previous treatment, the present material cannot be said to reflect the effect of penicillin alone, but only the effect of penicillin with or without fever therapy on a mixed group of cases with general paralysis, a significant but undetermined number of whom already had an at least partially arrested process when penicillin was first given. That this may detract from the

accuracy of the absolute percentages quoted cannot be gainsaid, but that it significantly affects their order of magnitude seems unlikely.

The present material was not found to be suitable for a biostatistically valid comparison of the effects of aqueous and repository penicillin. Relatively few patients received the long-acting preparations, and these were largely an ambulatory group. Among severe cases the results with repository penicillin seemed somewhat better than with aqueous penicillin, undoubtedly due to the difference in the type of patients treated rather than the type of penicillin used. It would appear, however, that repository penicillin is at least as efficacious as aqueous penicillin for the treatment of general paralysis. This conclusion has been amply borne out by our clinical experience with patients treated more recently than those included in the present study.

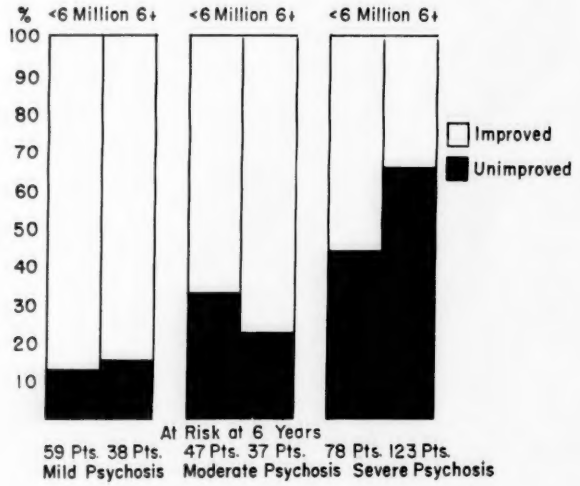

Fig. 10—Clinical status 6 years after treatment in relation to amount of penicillin.

In Fig. 10 is shown clinical status 6 years after treatment in relation to amount of penicillin given as study treatment. Consistent differences in clinical outcome could not be demonstrated. Likewise, consideration of work status and psychiatric institutionalization in these two treatment groups failed to reveal consistent differences. These data fit in well with the known extreme sensitivity of *Treponema pallidum* to penicillin. Although the present material does not permit a statement as to the minimal effective dosage of penicillin in general paralysis, it does permit of the pragmatically important conclusion that 6 million units is probably ample.

A comparison of the effect of penicillin alone with the effect of penicillin plus fever therapy is of utmost practical importance. Unless it can definitely be shown that there is meaningful additive effect, the markedly increased hazards and expense of fever therapy preclude its routine utilization.

In Fig. 11 is shown the clinical status 5 years after treatment in patients treated with penicillin alone and in patients treated with penicillin plus fever therapy. At 5 years after treatment the percentage improved was practically identical for the two treatment groups among the severe, moderate, and mild cases.

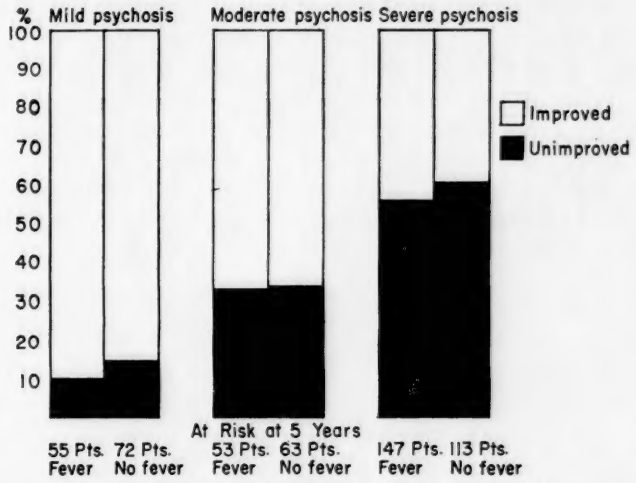

Fig. 11.—Clinical status 5 years after treatment. Penicillin versus penicillin plus fever.

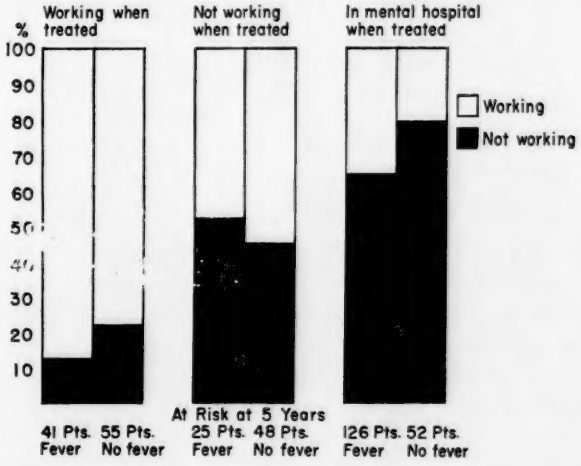

Fig. 12.—Per cent able to work 5 years after treatment. Penicillin versus penicillin plus fever.

In Fig. 12 there is shown the per cent of patients able to work 5 years after treatment among those treated with penicillin alone as compared with those treated with penicillin plus fever. Among the two groups of patients not in a

psychiatric institution at the time of treatment, consistent and significant differences in work status 5 years later were not observed. However, patients in a psychiatric institution when treated, who constituted numerically by far the largest group treated with fever, did better than similar patients treated with penicillin alone, 35 per cent as compared with 20 per cent having returned to work 5 years after treatment.

In general, as measured by the two yardsticks of clinical mental status and work or institutionalization status, it seems clear that the possible additive effects of fever therapy are not sufficient to justify its use in any significant number of patients. Yet, the individual clinician has some grounds for its use in selected cases—the avoidance of clinical Herxheimer reactions from penicillin when the use of this drug is delayed until the patient has had a paroxysm or two of fever; and the greater rehabilitation for work among fever plus penicillin-treated institutionalized patients.

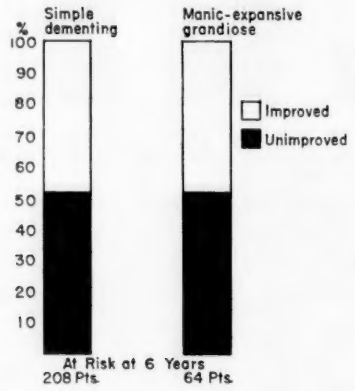

Fig. 13.—Per cent improved 6 years after treatment in relation to type of psychosis.

In Fig. 13 is shown the per cent of patients improved 6 years after treatment in relation to type of psychosis. As shown, outcome in these two groups was essentially identical with respect to per cent improved, but rehabilitation for work was achieved in almost half of the simple dementing group as compared with a little better than a quarter of the manic expansive grandiose group. Depressed patients did relatively well and paranoid patients least well, although in these groups the number followed was too small to allow of quotation of actual percentages. As expected, the small groups of patients diagnosed as paretic on somatic grounds alone and those with only questionable psychosis did well according to all criteria of outcome. It seems clear that type of psychosis is of less importance prognostically than is severity of psychosis, and that the patients with so little mental aberration as to fall into the "questionable" or "somatic only" categories have the best prognosis. The importance of early diagnosis and prompt treatment of general paralysis is thus once again demonstrated.

In Fig. 14 is shown the per cent of patients improved 5 years after treatment in relation to duration of paretic symptoms at time of treatment. As would be expected, patients with symptoms of less than one year's duration seemed to do slightly better than did patients with longer duration at time of treatment. Further subdivision of the former group yielded no consistent differences. It is felt that the actual differences are probably even more striking than the demonstrated ones and that the unreliability of historical data as obtained from paretics and/or their families may somewhat obscure these differences.

In Fig. 15 is shown the per cent of patients able to work 5 years after treatment in relation to duration of symptoms at time of treatment. The same general relationships are shown, with the ability to work inversely proportional to

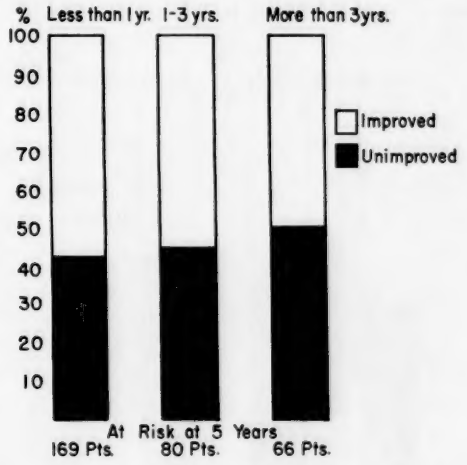

Fig. 14.—Per cent improved 5 years after treatment in relation to duration of paretic symptoms at time of treatment.

the duration of symptoms at the time of treatment. These data once again support the conclusion that early diagnosis and treatment afford a significantly increased prospect of clinical improvement, rehabilitation for work, and maintenance in or return to community life.

Outcome was considered in relationship to a number of other factors including age, race, and sex, educational level, chronic alcoholism, and the presence or absence of a Herxheimer reaction, Age, race, and sex had little influence on outcome, and chronic alcoholism and educational level almost none. Of particular importance is the question repeatedly raised in the past of possible permanent damage from the Herxheimer reaction. In the present material there is no evidence of such permanent damage other than the single death in status epilepticus. Indeed, patients who experienced either clinical or febrile Herxheimer reactions had a more favorable outcome as measured by clinical improvement or work status than did patients who did not experience the Herxheimer reaction. These differences may be in part due to the relatively small size of the Herxheimer

groups, but in part are due to the fact that Herxheimer reactions occur with greater frequency in patients with an active inflammatory process of the central nervous system, which has been shown to be more susceptible of improvement by treatment.

The present material, despite its size, was found not to be suitable for a detailed comparison of the value of repeated courses versus one course of penicillin. Many patients were given repeated courses as part of the original treatment plan without regard to any real indications for re-treatment. Others were re-treated for "insufficient improvement" even though the paretic process was apparently static, and still others received further treatment for other reasons. In all, 289 of the 1,086 patients were given more than one course of penicillin for one or another reason, but only 50 patients were re-treated for apparent clinical progression, of whom 45 had sufficient follow-up to provide a basis for analysis.

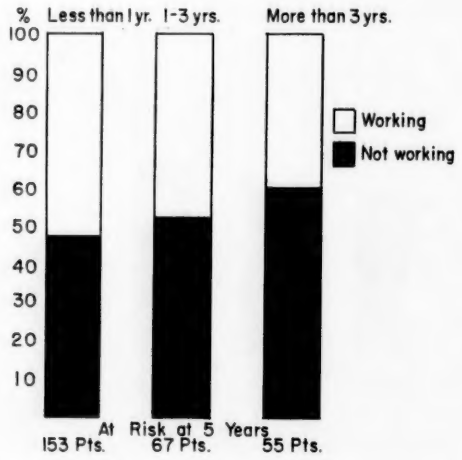

Fig. 15.—Per cent able to work 5 years after treatment in relation to duration of paretic symptoms at time of treatment.

Re-treatment seemed to benefit 14 patients who had improved after the initial course and subsequently had progressed, as only two of them were dead or institutionalized at latest observation. Re-treatment did not seem to benefit 31 patients who had not improved after the initial course, as 26 of them were dead or institutionalized at the latest observation. It is of interest that all of the 14 patients who had improved after the initial course of treatment did so on a dose of less than 6 million units of penicillin, only subsequently to progress. The paretic process in this group was obviously an active one, temporarily favorably affected by a subcurative dose and therefore susceptible of being arrested by re-treatment. In contrast, 16 of the 31 patients who had not improved after the initial course of treatment had received six or more million units of penicillin, suggesting that in this group the process was advanced and static and insusceptible of improvement by any amount of additional penicillin.

Since the presence or absence of the more frequent signs and symptoms of paresis was recorded both at the time of study treatment and at each post-treatment observation, it has been possible to evaluate the effects of treatment on these signs and symptoms individually, a matter of considerable importance to the physician dealing with these patients.

In Table V is shown the effects of treatment on individual signs and symptoms at the time of treatment. Significant numbers of patients were followed for 5 years. It should be clearly stated that in order to avoid, as far as possible, subjective bias and differences between examiners, no attempt was made to record improvement, but only complete disappearance of the sign or symptom in question. In view of this rather stringent interpretation, the effects of treatment upon the symptoms and signs of paresis as shown in Table V seem to be in general strikingly beneficent. Of considerable interest is the relative resistence of impairment of judgment, calculation, information, insight, and speech as compared with the other symptoms of paresis.

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TABLE V. EFFECT OF TREATMENT ON INDIVIDUAL SIGNS AND SYMPTOMS PRESENT AT TIME OF TREATMENT

50%-60% Cleared up at 5 Years	
Disorientation	Depression or euphoria
Convulsions	Untidy dress
Tremors	Incontinence
Inability to perform personal toilet	
40%-50% Cleared up at 5 Years	
Impaired memory	Impaired retention
Impaired handwriting	Delusions, hallucinations
Illogical conversation	Psychotic on simple obs.
30%-35% Cleared up at 5 Years	
Impaired judgment	Impaired calculation
Impaired insight	Impaired information
Impaired speech	

SUMMARY

Paresis strikes most frequently during life's most productive years. It is seen approximately three times as frequently in males as females, and over twice as frequently in whites as in Negroes. The usual incubation period is 10 to 24 years after infection. The simple dementing type of psychosis is more frequent than all other types combined. In the absence of previous treatment the spinal fluid complement fixation reaction is always positive and the spinal fluid cell count is almost always elevated. The blood serologic test may, rarely, be negative.

Penicillin prevents paresis. None of the present group of 1,086 patients had received penicillin for early syphilis. Paresis has not been observed to develop following the penicillin treatment of asymptomatic neurosyphilis.

The present study cannot be said to reflect the effect of penicillin alone, but only the effect of penicillin with or without fever therapy on a mixed group of paretics, a small but undetermined number of whom already had a process perhaps wholly or partly arrested by other types of therapy before penicillin was given.

The trend in recent years in the United States has been toward the treatment of paresis with penicillin alone. The possible additive effects of fever therapy are not sufficient to justify its use in any significant number of patients. The early diagnosis and prompt penicillin treatment of incipient paresis result in clinical remission and ability to work in more than 80 per cent of patients and will prevent practically all deaths from neurosyphilis. Even the severe or institutionalized patient has one chance out of three of improvement and rehabilitation for work. In contrast to the dire prognosis of untreated paresis only 9 per cent of penicillin-treated paretics are dead of paresis 10 years after treatment. Even so, the penicillin-treated paretic has nearly four times the death rate of his or her nonsyphilitic age, race, or sex counterpart.

The effects of treatment upon the individual signs and symptoms of paresis are in general strikingly beneficent. In the majority of cases, however, abnormalities of speech, insight, calculation, judgment, and general information do not entirely disappear.

Repository penicillin is quite as suitable as aqueous penicillin. Although the minimal effective dose is unknown, the present study suggests that 6 million units is probably ample.

In general, more than one course of penicillin is of no demonstrable additional value. Absence of clinical improvement, persistently abnormal spinal fluid protein level, or persistently positive spinal fluid complement fixation reaction are not indications for re-treatment. Re-treatment with penicillin is indicated under the following circumstances: an initial course of therapy of less than 6 million units, temporary clinical improvement following an initial course with subsequent clinical progression, or spinal fluid cell count of 5 or more after the first post-treatment year. The essentially identical probability of death in patients who receive one course and patients who receive more than one course of treatment is strong evidence against the value of routinely repeated courses of penicillin in the treatment of general paralysis.

Herxheimer reactions, notably exacerbation of the paretic psychosis or convulsive seizures, occur more frequently in the presence of spinal fluid pleocytosis than in its absence. The Herxheimer reaction does not appear to cause long-term damage.

Skilled neuropsychiatric examination affords definite prognostic data as to the probability of improvement in psychosis, rehabilitation for work, and to a certain extent as to death itself. Progression and death due to neurosyphilis occurred almost altogether in patients with "severe" pretreatment psychosis. Post-treatment psychiatric hospitalization was directly proportional, and clinical improvement and rehabilitation for work inversely proportional to the severity of pretreatment psychosis. Type of psychosis was of less importance prognostically. The shorter the duration of psychosis at the time of treatment the more

frequent was clinical improvement and rehabilitation for work. The presence at the time of treatment of incontinence, inability to perform simple acts of personal toilet, and of convulsions afforded a particularly poor prognosis for longevity.

Work status at the time of treatment was of great prognostic import, and of perhaps equal significance was the length of time which had elapsed since the patient had been able to work at his usual occupation.

Age, race, and sex were relatively unimportant factors in prognosis.

Pretreatment pleocytosis indicates an active inflammatory process more susceptible of improvement by treatment, but in a minority of patients leaving behind sufficient brain damage to nullify any real clinical effect. The absence of pleocytosis indicated a relatively static process less susceptible of improvement. Pretreatment spinal fluid protein levels were of less prognostic import. Persistent cell counts of 11 or more were for practical purposes not encountered after penicillin treatment. Clinical progression did, however, occur significantly more frequently with persistent cell counts of 5 to 10 than with cell counts of 4 or less. Persistent spinal fluid protein elevation was relatively frequent but of no prognostic import.

Considering the fact that as the incidence of syphilis itself decreases, dementia paralytica is becoming something of a neuropsychiatric rarity, the data which I have presented are perhaps of more historical interest than practical importance. They are, however, a dramatic illustration of the progress of medicine in four decades. A disease which was uniformly fatal within a few short years prior to Wagner von Jauregg's 1917 discovery of the efficacy of malaria therapy has now become curable in some, and partially remediable in many, by virtue of brief treatment with penicillin. The credit for this accomplishment is shared by your country through Fleming and Florey, and my own through Mahoney. Most of it belongs to Britain. May our future scientific and friendly brotherhood prove as profitable!

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ENERGY EXPENDITURE IN ASSISTED AMBULATION

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EARLY mobilization and ambulation following open reduction and internal fixation of fractures of the femur has become generally accepted as the treatment of choice in elderly people. Management of ambulation is usually conducted on an empiric basis, and no data are available as a guide in determining type or degree of assisted ambulation to be used in a specific case. The following study was undertaken to determine (1) the energy cost to the geriatric patient of ambulation with external support, (2) the type of assisted ambulation which produces the least expenditure of energy, (3) effects of assisted ambulation on the cardiovascular system, and (4) optimal duration of exercise periods.

Twenty patients with fractures of the upper femur were studied. Their ages ranged from 50 to 87 years, with a mean of 75 years. Selection of the participating patients was based only on their ability to cooperate and follow simple instructions. Sixteen of the group had clinical manifestations of moderate to advanced arteriosclerosis with some degree of cardiac and cerebral involvement. Four patients gave a history of cardiac failure and, of these, three were receiving digitalis at the time of testing. Two patients of the series were diabetic; one manifested early peripheral diabetic neuropathy, and the other presented moderately advanced diabetic retinitis and plantar callosities with ulceration. In the patients studied, there were 14 intertrochanteric fractures, 4 femoral neck fractures, and 2 subtrochanteric fractures. All had received previous instruction in the method of ambulation which they utilized and had had a variable period of training before testing was performed.

METHODS

Energy expenditure was measured by indirect calorimetry, using the lightweight (2.5 Kg.) portable respiratory meter of Kofranyi and Michaelis as modified by Müller.[1] The subject was observed in the postabsorptive state and free from current infection or acute illness. An Air Force half-face mask was carefully fitted, and expired air was conducted by means of valves and tubing to the respiratory meter, which the patient wore like a knapsack. A 10-minute observation was made, with the patient comfortably seated, to determine resting energy expenditure, and resting pulse rate and blood pressure were measured. The subject then walked for 3 minutes with crutches, walker, or parallel bars, and a

single observation was made of energy expenditure for a 6-minute period including 3 minutes of exercise and 3 minutes of recovery. Blood pressure and pulse rate were taken immediately after exercise. Finally, after a 15-minute rest period, a second 10-minute observation was made of resting energy expenditure, and resting blood pressure and pulse rate were taken again.

Ventilation was read directly from the meter, which had been calibrated with a 100 liter Tissot spirometer. Expired air was analyzed for oxygen content with a Pauling-Beckman analyzer.[2] Energy expenditure was calculated from ventilation and oxygen content of expired air, using the nomogram of Weir.[3]

The net rate of energy expenditure was calculated by combining the total expenditure in excess of resting requirement during exercise (current expenditure) with that during recovery (debt) and dividing by the number of minutes of exercise. Over-all rate was then taken as the net rate plus the resting rate. This method, the "integral method" of Müller,[4] was chosen over the "partial method," in which a sample of expired air is collected after a steady state is reached, and recovery (debt) is ignored. The integral method was used because of the inability of many subjects in this study to exercise long enough to reach a steady state. Thus the total energy expenditure (current plus debt) was measured. Oxygen consumption may remain slightly elevated for periods longer than the 3 minutes of recovery observed in this study, but since it declines exponentially, well over 90 per cent of the debt is repaid by 3 minutes at the rates observed.

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RESULTS

The average cost of assisted ambulation in this study was 2.82 Calories per minute of exercise, with a standard deviation of 0.78 Calories per minute of exercise. The individual values are presented in Table I. The mean energy cost of walking in parallel bars was slightly higher than for either of the other two modes of ambulation, but the difference was not statistically significant at the 5 per cent level as judged by t test.

Fig. 1 indicates the somewhat surprising fact that with walker and parallel bars, no significant difference was demonstrated in the energy cost of assisted walking with no weight on the affected leg. With crutches, partial weight-bearing appeared to require less energy, but again the difference was not significant at the 5 per cent level. The groups are small for statistical comparison, and larger numbers might bring out small differences, but, judging from the scatter in Fig. 1, such differences would not be of practical importance.

Almost all patients showed increases in systolic and diastolic blood pressure, pulse rate, and respiratory rate during exercise. In some instances the changes were negligible, but for certain individuals they were great enough to suggest a significant stress on the cardiovascular system. The changes in systolic blood pressure are represented in Fig. 2. Respiratory rate increased only moderately. The average increase of pulse rates was almost twice as great in the patients using walkers as in those using either of the other methods of ambulation, but again, the difference was not statistically significant. Certain individuals with rapid resting pulse rates were noted to show increases to rates above 120 per minute which were disproportionate to the rate of energy expenditure.

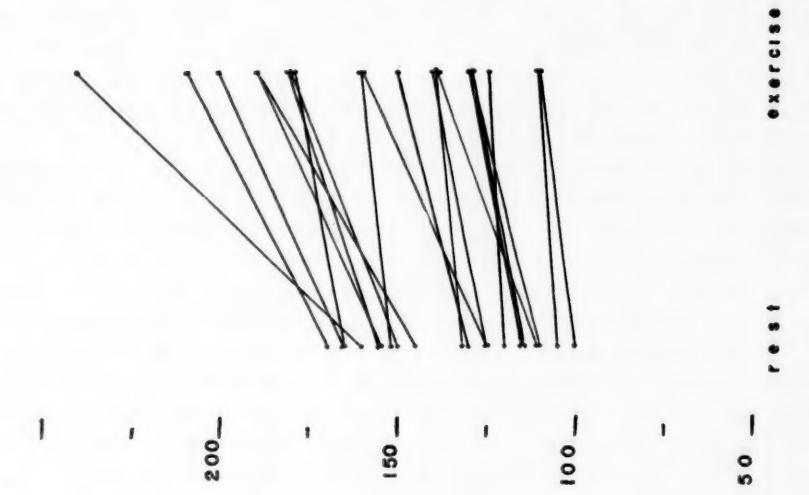

Fig. 2.

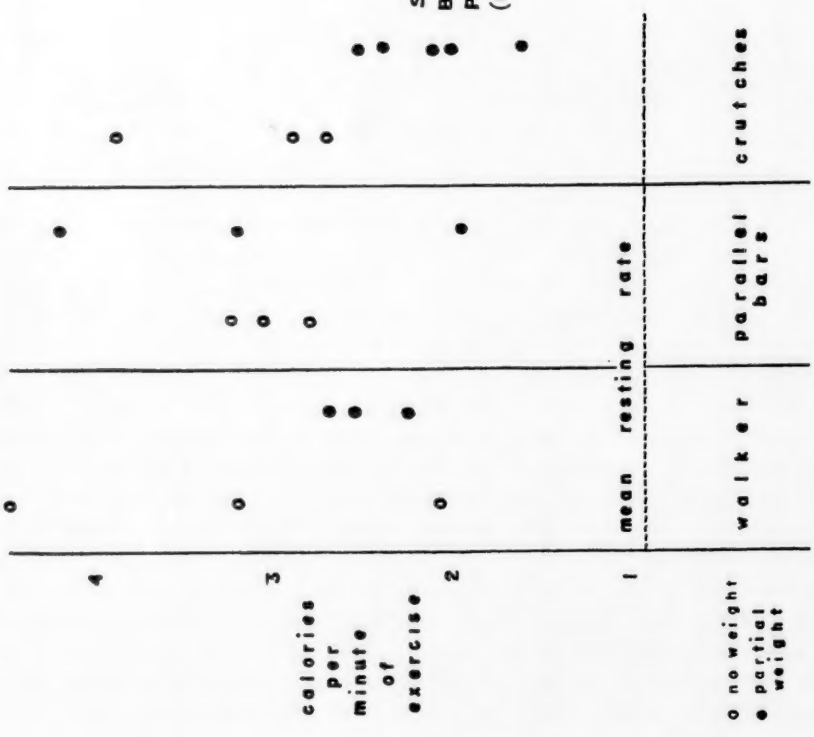

Fig. 1.

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TABLE I. PHYSIOLOGIC MEASUREMENTS DURING ASSISTED AMBULATION

SUBJECT	AGE	RESPIRATORY RATE		PULSE RATE		BLOOD PRESSURE		SURFACE AREA	ENERGY EXPENDITURE (CAL./MIN.)	
		REST	EX.	REST	EX.	REST	EX.		REST	EXERCISE
A. Walker (No weight-bearing)										
C. H.	75	26	28	70	108	115/60	130/65	1.57	.86	3.20
F. H.	75	23	24	66	98	115/75	180/80	1.55	.83	2.09
A. Z.	87	17	24	76	100	160/67	240/90	1.65	.93	4.55
Average	79	22	25	71	102	143/68	183/78	1.59	.87	3.28
B. Walker (Partial weight-bearing)										
C. N.	75	20	20	92	102	170/65	210/70	1.64	1.13	2.73
E. P.	74	21	24	80	102	125/70	140/90	1.56	.90	2.24
M. W.	83	23	26	108	108	145/90	190/90	1.59	.85	2.59
Average	77	21	23	93	104	136/75	180/83	1.59	.96	2.52
C. Parallel Bars (No weight-bearing)										
K. T.	67	18	20	83	94	134/100	140/100	1.52	.78	3.22
M. O.	79	30	30	90	110	110/65	140/70	1.81	.77	2.85
M. L.	78	22	22	107	126	152/80	160/80	1.42	.85	3.07
Average	75	23	24	92	110	132/82	146/83	1.58	.80	3.05
D. Parallel Bars (Partial weight-bearing)										
J. B.	65	20	22	84	80	165/100	180/100	1.83	1.08	4.28
M. B.	73	23	28	88	80	125/65	160/70	1.51	.96	3.28
M. G.	72	19	22	108	128	155/70	190/87	1.61	.93	1.99
Average	70	21	24	90	96	148/75	176/85	1.65	.99	3.18
E. Crutches (No weight-bearing)										
S. Z.	59	27	30	90	118	165/87	200/90	1.82	1.12	2.90
G. M.	60	29	22	85	88	115/70	130/90	1.65	.84	2.78
M. M.	83	15	18	74	110	110/65	130/70	1.84	.99	3.99
Average	67	20	23	83	105	120/74	153/83	1.77	.98	3.22
F. Crutches (Partial weight-bearing)										
B. J.	81	14	17	92	85	105/65	110/70	1.66	.88	1.88
C. A.	82	24	32	90	108	120/76	124/70	1.52	.68	2.16
J. B.	67	23	25	71	74	100/62	110/65	1.66	.95	2.49
J. C.	82	20	23	96	94	130/90	150/90	1.48	1.06	2.52
L. P.	82	20	23	84	84	150/80	180/90	1.41	.75	1.61
Average	79	20	24	85	89	121/74	135/75	1.54	.86	2.13

DISCUSSION

It would be desirable to compare the observed energy expenditure of these subjects with their maximum capacity and with the reactions of comparable control subjects. To force patients with the disabilities described to a true maximum exertion would, however, be unsafe. To assemble a control group, comparable in age and free from evident cardiovascular disease, would be possible, but to require such "normal" individuals to make use of assisted ambulation and to adopt partial weight-bearing gaits without extensive practice, would introduce many artifacts. Nevertheless, even in the absence of a satisfactory control group, we may gain some perspective by comparing the subjects of the present study with elderly "normal" individuals observed in other types of exercise.

The subjects of this study are comparable to their healthy contemporaries in terms of resting metabolic rate. Resting energy expenditure decreases with age. The mean and standard deviation for the 20 subjects in this study was 0.91 ± 0.11 Calories per minute, or 0.57 ± 0.07 Calories per square meter per minute, and their mean age was 75 years, with a range of 59 to 87 years. Considering the fact that these subjects were observed seated at rest rather than in the supine basal state, this figure corresponds well with the mean of 0.54 calories per square meter per minute for the basal metabolism of subjects aged 70 to 79 years given by Shock.[5] The average energy cost of assisted ambulation in this study, which was 2.82 Calories per minute, is therefore equal to three times the resting rate of energy expenditure.

The maximum sustained rate of energy expenditure which has been measured in man is 21 times resting level and represents long-distance running and cross-country skiing by expert athletes.[6,7] The maximum rate of energy expenditure which could be achieved by healthy, untrained young men on a treadmill was found by Taylor[8] to be approximately 14.5 times resting. Few measurements have been made of maximum energy expenditure on the part of healthy subjects in the age range represented in this study. Robinson[9] observed 8 men 59 to 71 years of age running on a treadmill at a rate judged to produce exhaustion in 5 minutes and found their mean energy expenditure to be 10.5 times resting level. Thus, it seems that the subjects of this study expended energy at a rate roughly equal to 30 per cent of the maximum rate of energy expenditure of which their healthy contemporaries are capable.

Enforced inactivity, excessive weight, and the use of an unnatural gait (partial weight-bearing) obtained in some or all of the subjects. These factors may all be assumed, from the work of other investigators, to lower the limit of maximum energy expenditure.[10,11,12] It is, therefore, probable that these patients were exercising close to their limits of tolerance. The impression that this exertion is close to the maximum for certain patients is further strengthened by the observation that two of the subjects developed pulse rates during ambulation of 126 and 128 per minute. In comparison, the pulse rates of the normal older men observed by Robinson during "exhausting" exercise ranged from 130 to 150 per minute at the end of 3 minutes. Subjectively, some of the subjects of the present study complained of exhaustion at the end of the 3 minutes of ambulation.

A simple guide to the desirable amount of exercise for an individual patient might be provided by observing the pulse rate immediately after a period of ambulation. If it did not exceed 120 per minute, and the patient did not complain of subjective exhaustion, the physician could safely increase the duration or frequency of exercise periods. Large increases of pulse rate, on the other hand, would serve as a warning that the current exertion was close to the patient's physiologic tolerance.

SUMMARY

The average energy cost of assisted ambulation in a group of 20 elderly patients convalescing from hip fractures was found to be 2.82 Calories per minute. This rate is approximately 30 per cent of the maximum energy expenditure for healthy men of the same age and may approach the actual maximum for certain patients. No significant differences in energy expenditure were demonstrated among patients using crutches, walkers, or parallel bars. Certain individuals showed marked increases of pulse rate or blood pressure during 3 minutes of assisted ambulation, and it is suggested that pulse rate may be used as a guide to the optimal duration of exercise in a specific case.

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PNEUMONITIS AS A COMPLICATION OF HEXAMETHONIUM THERAPY

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FOLLOWING the recent introduction of hexamethonium as an antihypertensive agent, several authors have reported a small number of patients who, while under hexamethonium therapy, developed a peculiar, progressive, and fatal pneumonitis.[1-6] In these patients, the organization of a fibrinous alveolar exudate and diffuse interstitial fibrosis advanced rapidly throughout both lungs leading to asphyxia and death. We wish to present another instance of this unusual complication of hexamethonium therapy in a young patient with chronic glomerulonephritis and severe hypertension.

CLINICAL DATA

A 22-year-old white male student was admitted to the Emory University Student Infirmary for the first time in October, 1955, for evaluation of his renal disease. The patient stated that in 1949, at the age of 16, he had "acute nephritis" manifested by hematuria, edema, headache, nausea, vomiting, and hypertension. After two months, the hematuria and edema subsided but mild proteinuria and hypertension of unknown severity persisted. Prior to his enrollment at Emory University, a physical examination in July, 1955, had revealed a blood pressure of 155/100 mm. Hg without other abnormal physical findings. Urinalysis at that time showed a specific gravity of 1.010 and 4 plus proteinuria. The hemoglobin, total serum protein, and blood cholesterol were normal. The N.P.N. was 52 mg. per 100 c.c.

On admission to the Student Infirmary, physical examination revealed a blood pressure of 240/160 mm. Hg. Except for a few small retinal exudates there were no other abnormal physical findings. The urinary specific gravity varied from 1.008 to 1.010 with constant 3 to 4 plus proteinuria. The hemoglobin, which had been normal 3 months ago, was now 11.3 Gm. per 100 c.c. and the N.P.N. had risen to 90 mg. per 100 c.c. P.S.P. excretion was 10 per cent in one hour. An electrocardiogram and chest roentgenogram were normal.

The patient was placed on a low sodium diet and started on 500 mg. of hexamethonium daily which was soon increased to 1,500 mg. per day. One week after the beginning of hexamethonium therapy, 100 mg. of hydralazine

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daily was added to the regimen. The blood pressure gradually fell to about 140/100 mm. Hg, and the patient was discharged with instructions to adjust the dose of hexamethonium and hydralazine according to his sitting blood pressure. He was followed as an outpatient.

The patient did quite well at first and attended classes until Jan. 20, 1956, when he developed chilliness and fever and was readmitted to the Student Infirmary. He reported that during the preceding 4 weeks he had noted a hacking cough with occasional expectoration of small amounts of yellow mucus. The blood pressure was 186/110 mm. Hg, and there was slight periorbital edema. Funduscopic examination showed "improvement." Moist râles were heard over both lung bases. The laboratory findings at this time included a total white blood cell count of 12,850 with 81 per cent neutrophils. The hemoglobin had dropped to 8.4 Gm. per 100 c.c. and the N.P.N. to 58 mg. per 100 c.c. Urinalysis and serum protein values showed no significant change. Chest roentgenograms showed a minimal amount of pleural thickening or fluid in both costophrenic angles, and there were linear densities in the left lower lobe suggesting pneumonitis. The patient was placed on tetracycline and the temperature gradually returned to normal, but the radiologic and physical findings in the left lung persisted. He was discharged after 6 days. While in the hospital, hexamethonium and hydralazine therapy was continued as before, and the patient was instructed to adhere to the same regimen while at home.

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Although the patient was still able to attend classes, he developed during the ensuing 2 months progressive shortness of breath, weakness, and weight loss. The previously noted pulmonary infiltrates progressed radiologically until they involved, in addition to the left lower lobe, both upper lobes and the left hilar reigon. About 2 months after the onset of respiratory symptoms the patient was again admitted to the Student Infirmary.

The temperature was 101° F., the pulse 96 beats per minute, and respirations were 22 per minute. The sitting blood pressure was 170/100 mm. Hg with marked postural hypotension. Coarse râles were heard over both lung bases, particularly on the left. Respirations were shallow, and he was unable to take a deep breath. There was marked exertional dyspnea without orthopnea, venous distension, or peripheral edema. Laboratory findings, including the N.P.N., were essentially unchanged from the previous admission. Five L. E. cell preparations and bacteriologic studies were negative. Roentgenograms revealed the presence of fluid over both lung bases and the bilateral pulmonary infiltrates were now associated with an increase in pulmonary artery markings.

Hydralazine administration was stopped on the day of admission but hexamethonium was continued as before. For the last 9 days of his life, the patient also received 80 mg. of prednisone daily. Despite all measures, including digitalis and anticoagulants, the patient remained febrile and his respiratory difficulties continued to increase. Terminally, electrocardiograms showed evidence for acute cor pulmonale. Dyspnea worsened, and the patient died on March 22, 1956.

At the time of death he was in his fifth month of continuous hexamethonium therapy and had experienced respiratory symptoms for about 3 months. Autopsy was performed 4 hours after death.

GROSS AUTOPSY FINDINGS

The body was that of a well-developed, poorly nourished, white man. The principal gross findings involved the lungs, kidneys, heart, and spleen.

The pleural cavities contained 200 and 250 c.c. of clear fluid each. The pleural surfaces were smooth and glistening and without adhesions except for the diaphragmatic surface of the left lower lobe where there was slight pleural thickening. The left lung weighed 400 Gm., the right 700 Gm. The lungs were voluminous, firm, and had a slightly irregular surface because of many 1-2 mm. subpleural emphysematous blebs. Virtually no crepitation could be elicited in either lung. The parenchyma looked and felt meaty with pink, frothy fluid oozing freely from the cut surface which had a gray and red mottled appearance. There were no discrete nodules, and the generalized induration involved all lobes of both lungs. The mucosa of the bronchi was smooth and glistening and except for some mucoid material the lumen was patent. The pulmonary arterial tree was free of thrombi or atherosclerosis. The hilar and mediastinal lymph nodes showed no abnormalities.

The peritoneal cavity contained 100 c.c. of clear fluid. The kidneys weighed 53 Gm. each and were similar in appearance. The capsule was thickened and firmly adherent to the underlying cortex. The exposed surface was studded with slightly elevated, grayish, 1-2 mm. areas on a pale brown background. The cortex varied from 3-4 mm. in thickness and was poorly demarcated from the medulla. The calyces, pelves, ureters, and renal vessels were not remarkable.

The pericardial cavity contained 200 c.c. of slightly cloudy yellowish fluid. The pericardial and epicardial surfaces were smooth and glistening. The heart weighed 407 grams (normal 344 grams). The right atrium and ventricle were moderately dilated, and there was left ventricular hypertrophy. The spleen weighed 264 grams and had a flabby consistency and dark red, soft parenchyma. The remaining organs were not remarkable. No permission had been granted for examination of the head and neck.

HISTOLOGIC FINDINGS

A progressive, organizing intra-alveolar and interstitial pneumonitis involved all lobes, severely altering the pulmonary architecture. Various stages of this process could be observed. Where the alveolar pattern was relatively intact, the alveolar surfaces were frequently lined by large cuboidal cells, and the lumen contained strands of fibrin and macrophages with or without brown pigment. Many groups of alveoli were filled by recent hemorrhage or masses of fibrin which extended to adjacent alveoli through the pores of Cohn (Fig. 1). In the more acute lesions the alveolar surfaces were often lined by a hyaline membrane which was slightly sudanophilic. Fat droplets were also demonstrable in some of the macrophages. The alveolar contents showed various stages of organization ranging from early ingrowth of fibroblasts to complete fibrosis (Fig. 2). The inflammatory reaction was generally mild. In the more acute areas, scattered neutrophilic polymorphonuclear leukocytes predominated while in the older lesions the response was largely mononuclear. The alveolar septa were generally thickened and showed fibrosis. They were infiltrated by scattered

mononuclear cells and contained occasional multinucleated giant cells without inclusions. No eosinophils were seen. In many areas of marked interstitial fibrosis, proliferation of the alveolar and bronchiolar epithelium formed glandlike

Fig. 1.

Fig. 2.

Fig. 1.—Acute lesion. Alveoli on right filled with fibrin and scattered polymorphonuclear leukocytes. Hyaline membranes on left. (Hematoxylin-phloxin, ×130.)

Fig. 2.—Chronic lesion with extensive fibrosis. (Hematoxylin-phloxin, ×120.)

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spaces. In these areas of complete obliteration of the pulmonary architecture, some arteries were large and tortuous, but their walls appeared normal. These vessels were noted to give rise occasionally to branches of precapillary size suggestive of dilated bronchopulmonary anastomoses. Elsewhere, the arteries and arterioles were of the usual caliber and showed intimal thickening and fibrosis but no vessel showed necrosis or inflammation. No old or recent thrombi were found. The pulmonary elastic tissue was generally decreased in amount and showed striking degeneration with fragmentation and clumping (Fig. 3). The elastic membranes of the small arteries were split and fragmented, while those of the large tortuous vessels seemed intact. The bronchi showed mild chronic inflammation and fibrosis, but there was no evidence of bronchiectasis or bronchopneumonia. In the areas of severe parenchymal fibrosis the bronchi could not be definitely identified.

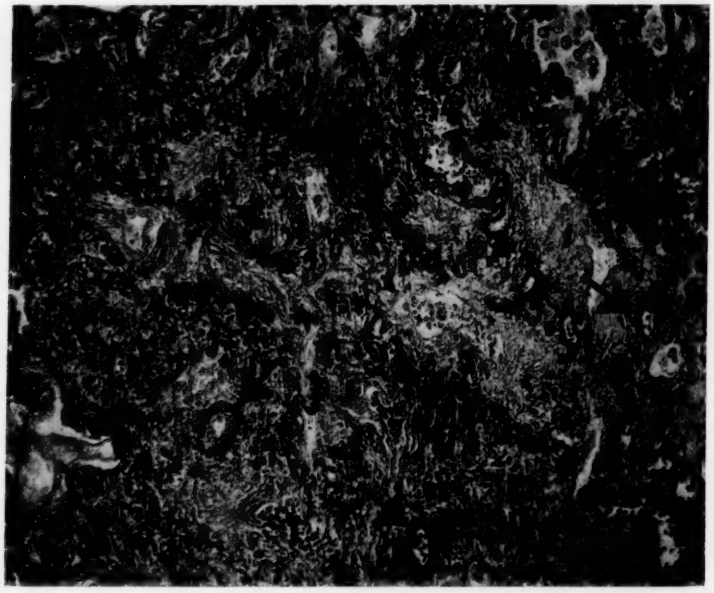

Fig. 3.—Marked degeneration of parenchymal and vascular elastic tissue. Note vascular changes (arrows). (Weigert's elastic tissue stain, ×125.)

The kidneys showed extensive fibrosis and mild diffuse chronic interstitial inflammatory cell infiltration. Multiple sections revealed no completely normal glomeruli. The glomerular changes ranged from focal or diffuse thickening of the glomerular stroma to adhesion formation and, finally, complete hyalinization. The glomerulonephritis appeared inactive. While some tubules were atrophic and contained hyaline casts, others were widely dilated, tortuous, and lined by large eosinophilic cells with finely granular cytoplasm which contained rare vacuoles. The arterioles frequently showed intimal thickening and laminated fibrosis of the wall while the larger arteries revealed only patchy mild intimal thickening. There was no necrotizing arteriolitis. The remaining organs were

not remarkable except for marked congestion of the spleen and adrenocortical lipoid depletion. There was no significant generalized atherosclerosis or evidence of other vascular disease.

FINAL ANATOMIC DIAGNOSES

Diffuse pulmonary fibrosis, probably due to hexamethonium
Chronic glomerulonephritis
Myocardial hypertrophy (407 Gm.)
Pericardial, pleural, and peritoneal effusion
Cor pulmonale

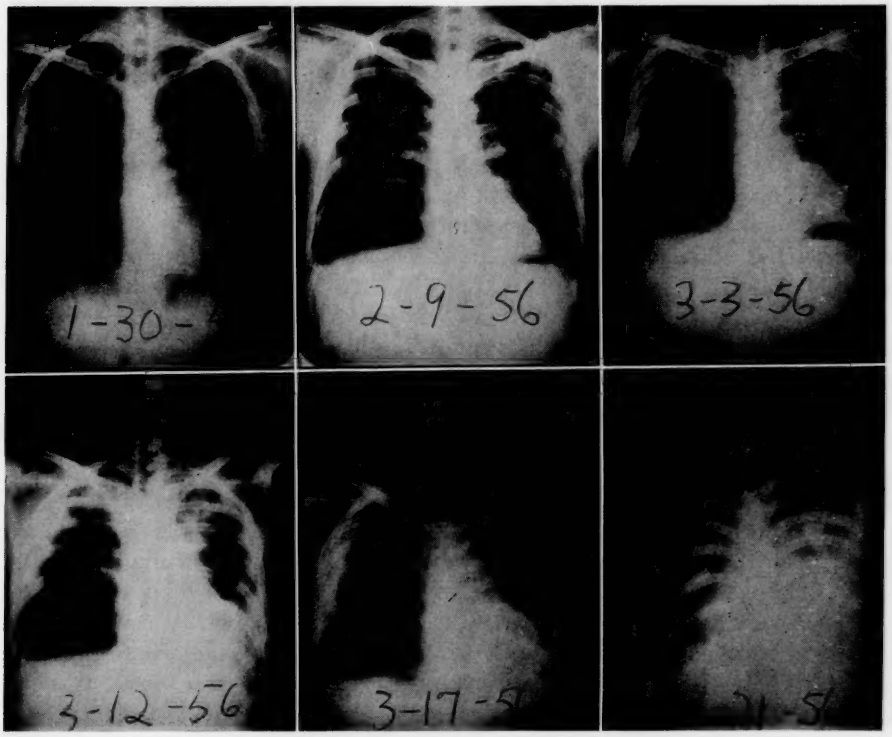

Fig. 4.—Consecutive chest roentgenograms covering a 52-day period. Final film taken one day before death.

DISCUSSION

This young man with chronic glomerulonephritis, severe hypertension, and no previous lung disease died of respiratory insufficiency 3 months after the onset of pulmonary symptoms. The rapid progression of the lesions is illustrated in Fig. 4. Hexamethonium therapy for hypertension had been instituted 5 months prior to death, and hydralazine was later added to the regimen. The therapeutic response was good as evidenced by a lowering of the blood pressure

and some regression of eyeground changes. Except for postural hypotension, treatment was well tolerated and the patient was able to attend classes regularly. However, the findings of proteinuria, mild azotemia, and low urinary specific gravity persisted unchanged. After 2 months of drug therapy he developed at first a mild cough which was followed by anorexia, weakness, and, one month later, by a low-grade fever and progressive respiratory difficulties which finally led to death. While hydralazine administration was discontinued 2 weeks before death, hexamethonium therapy was maintained throughout. Autopsy showed advanced chronic glomerulonephritis without evidence of recent activity or morphologic evidence of uremia. The lungs revealed an extensive, progressive, organizing, intra-alveolar, and interstitial pneumonitis which readily accounted for the patient's respiratory difficulties. Large portions of the pulmonary parenchyma were replaced by fibrous tissue. In addition, there was a diffuse degeneration of the elastic tissue including that of the arterioles. An increased resistance to pulmonary arterial blood flow was indicated by the findings of a cor pulmonale, pulmonary artery sclerosis, and the presence of dilated, hypertrophied vessels, probably representing bronchial arteries, which have been described in lungs with various types of pulmonary artery obstruction.[7]

The pulmonary fibrosis in our patient cannot be related on clinical or morphologic grounds to pre-existing chronic lung disease, lipoid pneumonia, or microbial or fungus infection. An organizing pneumonia of viral origin involving the entire pulmonary parenchyma and leading to death in respiratory insufficiency appears unlikely. The patient showed no signs of congestive heart failure such as orthopnea, peripheral edema, and increased venous pressure. In addition, the morphology of the pulmonary changes indicates a degree of abnormal capillary premeability which is not seen in congestive heart failure. The lesions, however, show a morphologic similarity to the so-called uremic pneumonitis but differ from this entity by the diffuse involvement of both lungs culminating in death from respiratory insufficiency. This case, however, fits well into a small group of patients with a similar pneumonitis appearing during hexamethonium therapy. All these patients had severe hypertension invariably associated with mild azotemia but not uremia. In some cases the underlying disease was malignant hypertension while others had chronic glomerulonephritis. Therapy with hexamethonium alone or together with hydralazine always lowered the blood pressure but after a few weeks or months, signs of progressive respiratory insufficiency appeared. None of the patients developed uremia or congestive heart failure. The pulmonary lesions appeared related only to the use of hexamethonium and, to our knowledge, have not been reported in patients treated with other ganglion-blocking agents. There was no evidence of hydralazine toxicity and the pulmonary findings in those patients who had received hexamethonium alone were quite similar to those receiving both drugs. It has, therefore, been assumed by some[1,2,4-6] that this type of pulmonary disease represents a rare complication of hexamethonium therapy.

No satisfactory explanation of the pathogenesis of this type of pneumonitis has been advanced. Doniach, Morrison, and Steiner[3] believed that the lung changes are the result of prolonged pulmonary edema during attacks of congestive heart failure in hypertensive patients whose life has been prolonged by

hexamethonium therapy. Viersma[5] feels that the lung changes may be the indirect result of the ganglion blocking effect of hexamethonium which leads to excessive pooling of blood in the pulmonary circulation. Perry, O'Neal, and Thomas[6] note the resemblance of the lesions to uremic pneumonitis and suggest that in the absence of uremia, methonium salts may have the same effect on the lung as nitrogen retention. The dosage of hexamethonium in the reported cases of pneumonitis varied greatly and cannot be related to the development of the pulmonary lesions. Where the authors indicate the duration of hexamethonium therapy, 15 of a total of 16 patients were treated for less than 6 months, and 9 of them for less than 4 months. This includes our case. It seems, therefore, that this complication tends to occur early in the course of hexamethonium treatment.

The striking alterations of the elastic fibers in the parenchyma and arterioles of the lung which our patient presented have not been stressed previously. The possible significance of this finding cannot be evaluated at this time. It may merely be the result of progressive parenchymal injury during the development of the pneumonitis but could also be the primary lesion of hexamethonium toxicity in hypertensive and azotemic patients whose blood pressure has been lowered by therapy.

Adrenocortical steroids and other medications do not appear to have helped in our case. It is conceivable that early recognition of this uncommon complication of hexamethonium therapy followed by cessation of the drug may arrest the progression of the pneumonitis. This condition should be suspected in any azotemic but not uremic patient whose blood pressure drops as the result of treatment with hexamethonium and who develops after a few weeks or months pulmonary symptoms with physical and roentgenologic signs of a progressing diffuse pneumonitis which cannot be explained by infection or congestive heart failure.

SUMMARY

A diffuse, progressive, organizing intra-alveolar and interstitial pneumonitis was found at autopsy to be the cause of death in a hypertensive patient with chronic glomerulonephritis treated with hexamethonium. A striking degeneration of the pulmonary parenchymal and vascular elastic tissue was observed.

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Review

THERAPEUTIC CONCEPTS RELATING TO HYPOTHYROIDISM IN CHILDHOOD

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PHYSICIANS in the late nineteenth century, observing the dramatic effects of administering crude preparations of whole thyroid gland, hopefully considered the problem of hypothyroidism solved. Their optimism was portrayed by the comments of William Osler who, in 1894, in a classic presentation and review of sporadic cretinism on this continent stated, "Not the magic wand of Prospero or the brave kiss of the daughter of Hippocrates ever effected such a change as that which we are now enabled to make in these unfortunate victims, doomed heretofore to live in hopeless imbecility, an unspeakable affliction to their parents and to their relatives."[1]

Unfortunately, Osler's optimism has not been confirmed.[2-15] It is the purpose of this publication to emphasize that early diagnosis and adequate therapy are necessary for the congenital hypothyroid child to achieve his potential central nervous system growth and development and to present clinical and laboratory features of thyroid deficiency which will aid the physician to achieve this early diagnosis and adequate treatment.

Mental deficiency in hypothyroid children is suggested by some workers to be due to abnormal central nervous system development in utero which is of similar congenital origin as the thyroid aplasia but need not be due to hormone deficiency. This hypothesis seems unlikely for several reasons:

1. Investigations of the mental ability of parents and siblings of cretins have failed to reveal that they have a greater than normal incidence of mental deficiency.[3-5,7]
2. Among discordant monozygotic twins with cretinism, the cretin members bear classical features and stigmata of the disorder while their parabionts are normal.[16-20]
3. In sporadic familial goitrous hypothyroidism, which is to be contrasted with nongoitrous sporadic congenital

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hypothyroidism because it is an inborn error of metabolism transmitted by a recessive autosomal gene and because it need not always be manifest in early infancy, relationships between thyroid deprivation in early infancy and early adequate treatment and mental deficiency are much the same as observed in the classical sporadic nongoitrous, nonhereditary familial form of cretinism.[21-26]

4. Relationships between mental deficiency and treatment are also similar when one compares sporadic and endemic cretinism.[27-29]
5. An increased incidence of other congenital anomalies has not been observed in sporadic cretinism.

The major role of thyroid hormone in the growth and development of the central nervous system has been shown by experimental and clinical observations. Experimental thyroid deficiency in the monkey and in lower mammals, induced at birth and sustained through early life, produces irreversible histologic and functional changes in the central nervous system similar to those observed in human cretins.[30-38] (Table I.) The brains of such animals are grossly deficient

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TABLE I. STUDIES IN NORMAL AND ATHYROID INFANT MONKEYS DURING FOUR MONTHS OF THYROXINE THERAPY (30 TO 150 DAYS OF AGE)

GROUP	THYROXINE γ/KG./DAY	S.H.I. γ%	CALORIC INTAKE CAL./KG./DAY	WEIGHT GAIN GM./KG./DAY	BONE GROWTH AND DEVELOPMENT		BRAIN GROWTH§
					EPIPHYSEAL CENTERS†	FEMUR AND TIBIA GROWTH‡ CM./30 DAY	
Athyroid*	0	2	100	1–2	−4 to 5	0 to 0.1	Minus 35%
	5–6	4–6	200–250	4–5	−4 to 5	0.2 to 0.3	Minus 35%
	15–20	7–12	250–300	6–8	Normal	0.5 to 0.7	Normal
Normal	0	6–9	250–300	6–8	Normal	0.5 to 0.7	Normal

*I^{131} thyroid ablation at birth; confirmed at 30 days.
†One-half of skeleton counted every 30 days (technique of Sontag).
‡Long bone survey for length every 30 days (technique of Lusted).
§Brain weight at sacrifice (150 days).

in weight and have histologic evidence of abnormal vascularity, deficient myelinization, and degenerative and atrophic changes of neuronal and interstitial components. Unless specific substitution therapy is instituted soon after thyroid ablation, these pathologic changes are irreversible, and functional impairment persists.[38] (Table I.) In the rat, similar changes follow hypophysectomy; prevention cannot be accomplished in this preparation without administration of thyroxine.[35]

There appears to be little doubt that thyroid deficiency in humans sustained through early infancy produces similar changes; moreover, there is reasonable

correlation between the early introduction of an adequate program of substitution therapy and final mental development.[12,13,15] A review of central nervous system growth and development shows that the infant is maximally subject to central nervous system damage due to thyroid deficiency during the first weeks or months of life. The rapid rate of brain growth and development characteristic of intrauterine life continues during early postnatal life. Seventy to 75 per cent of total brain growth is extrauterine; and, of that, almost one-half occurs by 5 or 6 months of age and two-thirds by the age of 1 year.[39,40] Severe central nervous system retardation seldom occurs if the thyroid deficiency is acquired after 2 years of age.[5,11-15] The occurrence of thyroid hormone deficiency in utero, though theoretically capable of causing very severe damage, is unlikely. In the presence of a normally functioning placenta in an euthyroid mother, the maternal fetal transfer of thyroxine appears to be capable of maintaining normal growth and development of an athyroid fetus or infant in utero. In the majority of instances, athyroid infants have no apparent hormonal deficiency until hormone existing at the time of birth undergoes several utilization half-lives. This usually requires from 1 to 3 weeks. No significant quantitative difference has been observed in studies comparing the concentration of serum hormonal iodine in maternal and cord blood, despite the fact that a greater percentage of circulating thyroxine is bound to the thyroxine-binding protein in maternal sera.[41-45] Theoretically, this increase in maternal protein-bound thyroxine and proportional increase in maternal hormone production should augment a relatively increased effective hormone concentration in fetal tissues as compared to maternal tissues. In the few cases in which sporadic cretinism has been manifest at birth, mental deficiency has been severe and has seemed proportionate to the estimated duration of intrauterine hormone deficiency.[12,15]

The suggested clinical importance of an adequate program of substitution therapy has been substantiated experimentally in this laboratory through studies of athyroid infant rhesus monkeys maintained for prolonged periods on varying doses of Na-l-Thyroxine. A tabulation of studies relating to thyroxine dosage, serum BEI concentration, caloric intake, body weight gain, skeletal growth and maturation, and brain development is presented in Table I.

While athyroid animals receiving 5 to 6 mcg. per kilogram daily Na-l-Thyroxine appeared relatively normal, growth and development of their skeletons and brains were significantly retarded; in contrast, growth and development of the skeletal and central nervous systems were normal among other athyroid infant animals receiving 15 to 20 mcg. per kilogram a day Na-l-Thyroxine.[46] It is of interest that athyroid infant animals carried to adulthood on the larger doses of hormone have remained normal in all respects. Various additional metabolic studies relating to energy metabolism, liver, cardiovascular and renal function have served to strengthen the more important point that many functions can be near normal while significant deficiency may exist with respect to the skeletal and central nervous systems. Such studies, correlated with BEI values resulting from the various levels of thyroxine therapy employed, are graphically presented in Fig. 1. Variable responses of organ systems to therapy with thyroxine in relation to SHI* values are given.

*Serum hormonal iodine (mcg. per cent).

These studies have clinical implication in view of the commonly observed general growth lack and specific delay in skeletal growth and development among athyroid human infants and children "treated" for prolonged periods. It is unfortunate that the amount of hormone necessary to reverse major physical signs and to return gross metabolism to nearly normal levels is inadequate to promote normal skeletal and central nervous system growth and development.[13,46] This seeming discrepancy in tissue responsiveness to a given dose of hormone could well relate in part to features of distribution and decay of thyroxine released to the blood stream by the thyroid. In studies of distribution and decay of thyroxine, conducted on athyroid and normal immature rhesus monkeys in this laboratory,[47] it has been observed that available thyroxine ultimately assumes a volume of distribution equal to that of body water. Moreover, the time required for this distribution is only twice that required for biologic degradation (utilization). These data are presented in Fig. 2.

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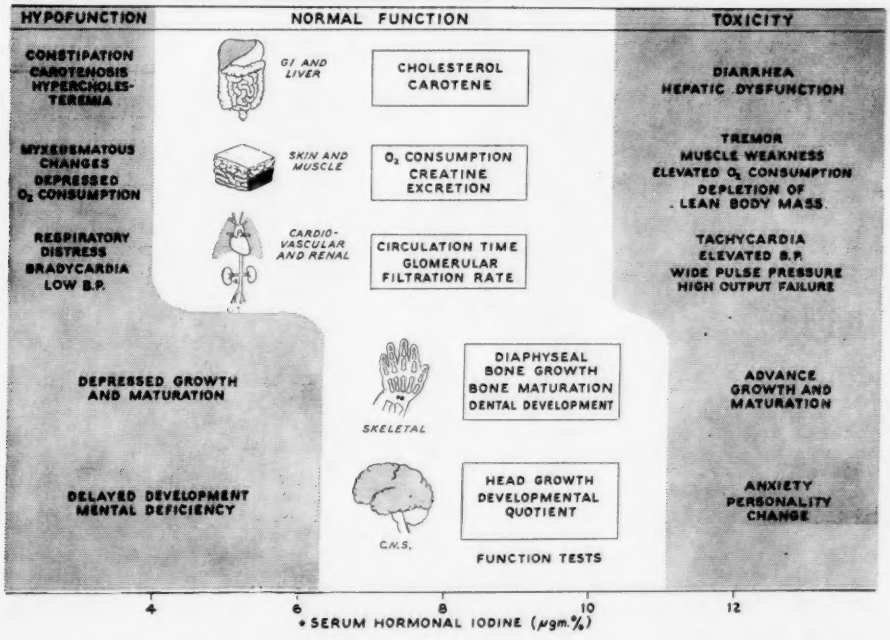

Fig. 1.

While the majority of existing clinical reports provide an ample body of information confirming the association of poor mental development with delayed and/or inadequate therapy, there is but scattered evidence demonstrating the improved mental development which occurs with early introduction of adequate substitution therapy. There are three major reasons for this unfortunate situation.

1. It is common practice to begin treatment of the athyroid infant with homeopathic doses of dessicated thyroid (1/10 to 1/4 grain a day). Gradual

increases are made at intervals. This practice prolongs severe hypothyroidism for 3 to 6 months or more when the growth and development of the central nervous system is normally maximal; moreover, this time has routinely been included as a part of the "therapeutic" period in most studies when in reality it should not be. The origin of this untimely practice has no doubt been inherited from adult medicine or stems from the past when cretins went untreated for many years, and its dissemination has been medicated by the textbook.

2. "Adequacy" of therapy has usually been a subjective impression and has rarely been reduced to exacting objective criteria. For example, many authors report persistence of retarded skeletal development and growth and other signs of inadequate therapy even after long periods of treatment.

3. A standard technique for evaluation of mental development has not been agreed upon; consistency is often lacking in individual reports.

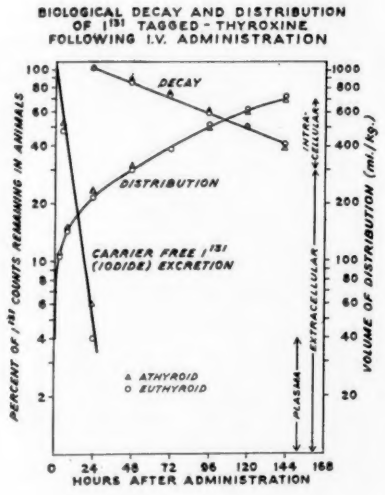

Fig. 2.

The authors propose that a reasonable proportion of any lack of confidence which might exist (relating early adequate treatment and normal mental development) reflects to a large extent the fact that reporting physicians have included this initial, variably long, homeopathic period of treatment as a part of their statistic. Use of wholly adequate doses of hormone from the time of diagnosis could well improve confidence.

CLINICAL COMMENTS

While endemic cretinism is uncommon in the United States, certain of its features warrant discussion. Its appearance in infancy may be associated with a pregnancy complicated by goiter, and the infant may appear cretinoid at birth due to intrauterine thyroid hormone deficiency. Goiter in a pregnant patient,

either developing during or antedating the pregnancy, is likely to be due to thyroiditis, latent or evident thyrotoxicosis, malignancy, or familial goitrous hypothyroidism; and investigation to determine the cause is necessary. The treatment of choice for the goitrous pregnant female will depend upon the etiology of her condition and factors relating to fetal thyroid physiology. Hypothyroidism during pregnancy, irrespective of etiology, must be adequately treated with thyroxine or dessicated thyroid to protect the fetus.

Fetal thyroid function, as measured by I^{131} uptake, occurs when there is organization of the glandular elements and appearance of thyroid follicles containing colloid. This has been shown to exist by 14 to 32 weeks of pregnancy.[48,49] Use of I^{131} or thiourea derivatives in pregnant women is capable of causing fetal thyroid damage. The authors have observed one case and are aware of two others in which severe thyroid damage to the fetus followed therapeutic use of I^{131} during pregnancy. Use of I^{131} should also be avoided in lactating mothers bebecause of its high concentration in breast milk following such a procedure.[52] Administration of goitrogens to pregnant females can also cause fetal thyroid damage.[50,51]

The remainder of this discussion will deal principally with clinical and laboratory features of the types of thyroid deficiency commonly encountered in children on this continent. Sporadic congenital hypothyroidism is divided into (a) sporadic congenital athyrosis, and (b) sporadic familial goitrous hypothyroidism. Of these two entities, nongoitrous congenital athyrosis occurs 10 to 20 times more frequently than sporadic familial goitrous hypothyroidism.[1,21,26,53] The exact etiology of thyroid agenesis in sporadic nongoitrous cretinism is not known; however, its occurrence in one of monozygotic twins indicates that rather than being genetically conditioned, it is related to the direct influences of environmental factors on the development of the thyroid anlage in the fetus.[16-20] The near absence of familial coincidence in athyrotic sporadic cretinism lends further support to that hypothesis.

Sporadic familial goitrous hypothyroidism is an inborn error of metabolism transmitted by a recessive autosomal gene and may occur in up to 50 per cent of offspring in a family. It is to be differentiated from endemic cretinism with goiter, a condition in which a genetic prediposition has been clearly ruled out.[54] Thyroid deficiency in sporadic familial goitrous hypothyroidism may be severe and appear in early infancy, or may be of minimal severity and appear as late as the second or third decade. The age at which the goiter appears and its microscopic pathology are variable and depend on the degree of thyroxine deficiency as well as the potentiality of the gland for hyperplasia.[26,55] Hypothyroidism appears very early and is usually, but not always, associated with a rapidly growing, diffuse goiter when the error in hormone synthesis is near complete and the gland is comprised of responsive tissue. In the presence of a minimal amount of responsive tissue, goiter does not appear until late in childhood, even with severe impairment of hormone synthesis. In some instances, deficiency of hormone synthesis by the thyroid may not be severe and hypothyroidism may be delayed until later childhood and usually follows the slow development of a goiter.[26,55]

The essential abnormalities of iodine metabolism in this condition resemble those which follow administration of goitrogens such as thiourea and derivatives.[56]

It is postulated that the defect in hormone synthesis may represent a deficiency in the effective concentration of oxidative enzyme (s) responsible for the oxidation of thyroid-trapped iodide. This oxidation is necessary to iodination of tyrosine and important to final precursor linkage.[26,56] It is also of interest that these children do not dehalogenate iodotyrosines, either in thyroid or peripheral tissues.[57-59] This defect in the thyroid gland leads to the rapid appearance of iodotyrosines in plasma; moreover, lack of dehalogenation by extra thyroidal tissues results in their abnormal and rapid appearance in urine and prevention of a normal recycling of iodide within the body.[57-59] Recycling of iodide by the thyroid and by the body as a whole is important in normal iodine metabolism. It is felt that, along with tri-iodothyronine and thyroxine, mono- and di-iodotyrosine are included in the process of hormone mobilization and that the latter substances are normally deiodinated before release by the gland.[59,60]

Clinically applicable features of the disturbed metabolism in these patients are summarized below:

1. The thyroid iodide-trapping mechanism in sporadic familial goitrous hypothyroidism is normally responsive, and patients with that disorder typically have an accelerated I^{131} uptake. This is in contrast to the reduced or absent I^{131} uptake by nongoitrous cretins. The increased I^{131} uptake and a significant proportion of thyroid gland enlargement is presumed secondary to TSH (pituitary thyroid stimulating hormone) excess in the untreated case.[21-26,62,64]

2. Even though the hormone precursors mono- and di-iodotyrosine may be synthesized in sporadic familial goitrous hypothyroidism, synthesis of thyroxine is inadequate.[23-26,55,62-64] There is a deficiency of circulating thyroxine which leads to increased pituitary TSH release, and secondarily to thyroid gland hypertrophy and hyperplasia (goiter).

3. The compensatory chain of events resulting from the defect in hormone synthesis can be prevented by therapy with adequate amounts of thyroxine (that is, such therapy leads to TSH suppression, reduced I^{131} uptake, and disappearance of goiter). Goiter should not appear under conditions of adequate therapy, instituted and sustained from infancy.[25,26]

4. Systemic thyroid deficiency is the most significant clinical feature of sporadic familial goitrous hypothyroidism, and its general effects on growth and development in no way differ from those observed in any other thyroid-deficient infant or child.

The etiology and incidence of acquired hypothyroidism in infancy and childhood are unknown except when they are the result of toxic action of various drugs (more recently including cobalt and Butazolidin), acute systemic infections, thyroiditis, surgery, or inadvertent exposure to radiation. It may well be that a fair per cent of children who become hypothyroid in later infancy or early childhood are examples of sporadic familial goitrous hypothyroidism and would ultimately develop goiter if therapy were withheld or inadequate for sufficient time.[26]

It is equally plausible that many reported cases of "mild" congenital athyrosis may represent acquired thyroid damage. Certainly every possible etiologic factor should be considered in such children, and final diagnosis made as specific as possible.

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CLINICAL SIGNS OF THYROID PRIVATION

With an important few exceptions, the clinical signs and symptoms of thyroid deficiency in early infancy vary only in degree from those seen in older children.[13] Striking respiratory distress, including episodes of frank cyanosis, is often a major sign, and infants may gradually assume a position of opisthotonus to help maintain an adequate airway as myxedema of the tongue and para- and retropharyngeal tissues develop. The respiratory distress often leads to investigation for possible "thymic enlargement" or congenital cardiorespiratory anomalies. Related signs and symptoms include: a hoarse, low-pitched cry; progressive difficulty in ability to swallow, and disinterest in food; persistence of "physiologic" jaundice; little progress in motor or psychologic achievement; sluggish, diminished reflexes; and persistence of immature neurologic features.

Dwarfing and continuing infantile proportions and delayed dentition are apparent only as normal growth fails to occur; and if they are present in a congenitally athyroid infant or an infant with familial goitrous hypothyroidism at the time of diagnosis, a valuable period for treatment has been lost because early infancy is the period of the most rapid growth and development of the brain. Serious compromise of intellectual development is likely to occur. The development or even partial persistence of these signs in an infant under treatment implies that therapy is grossly inadequate and similar consequences are likely.

Other signs of thyroid deficiency in infancy are of variable intensity and not too unlike those seen in the older hypothyroid child; these include hypothermia, diminished circulation, slowed pulse, decreased pulse pressure, diminished sweating, dry thickened skin, and umbilical hernia. An adequate classification of these and related features according to organ systems is shown in Fig. 1.

In children untreated or inadequately treated through early infancy, variable degrees of mental retardation usually exist in association with various behavior and neurologic aberrations including speech disorders, short attention span, and defective abstract reasoning. Spasticity, tremors, and EEG changes may also occur.[4,9,15,65]

Patient photographs are presented to show physical variations in hypothyroid infants and children. Fig. 3 shows double-ovum twins, aged 4½ months. The infant on the right is an obvious cretin. These children were of equal size and appeared normal to the attending physician and parents at birth and during the neonatal period. By the age of 3 to 4 weeks the cretin member was feeding poorly, had become lethargic, and had begun to manifest many early signs of thyroid deficiency. By the age of 5 to 6 weeks these signs were nearly as severe as demonstrated in the illustration, and differences in growth between the twins had become significant. Note that the cretin twin demonstrates persistence of newborn hair, macroglossia, cretinoid facies, and umbilical hernia.

This case serves to emphasize the fact that no one symptom or any combination of signs or symptoms leads to the diagnosis and that physicians must have a high index of suspicion for possible thyroid disease when, either by history or by physical examination, an infant is found to manifest primary and secondary effects of depressed metabolism and growth.

Fig. 3.

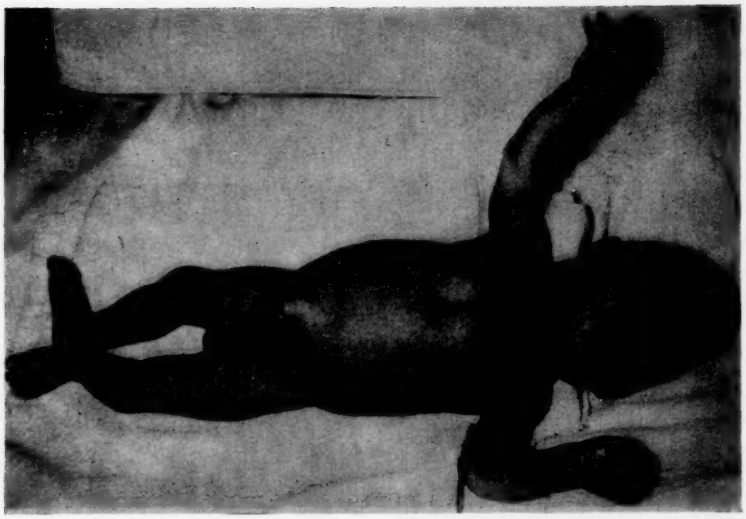

Fig. 4.

In Fig. 4 a 6-month-old untreated cretin demonstrates many of the signs of thyroid privation usually obvious by 3 to 6 weeks of age: persistence of sparse infantile hair, low brow, poor development of the nasal bridge, macroglossia,

short bull-like neck, abdominal protruberance, and umbilical hernia. At the time the photograph was taken, the child was in the process of the Moro reflex. Interestingly enough, he had been considered a probable example of congenital cardiorespiratory anomaly for some time and was admitted to the cardiac service of the university hospital with that as a tentative diagnosis.

At the time of photographing, this infant had acquired a very significant growth deficit with relatively greater deficiency in linear growth of the long bones than of the torso and, therefore, presented a picture of exaggerated infantile proportions.

Despite the introduction of a program of treatment which rapidly reversed major growth and metabolic signs of thyroid deficiency, marked mental retardation has persisted.

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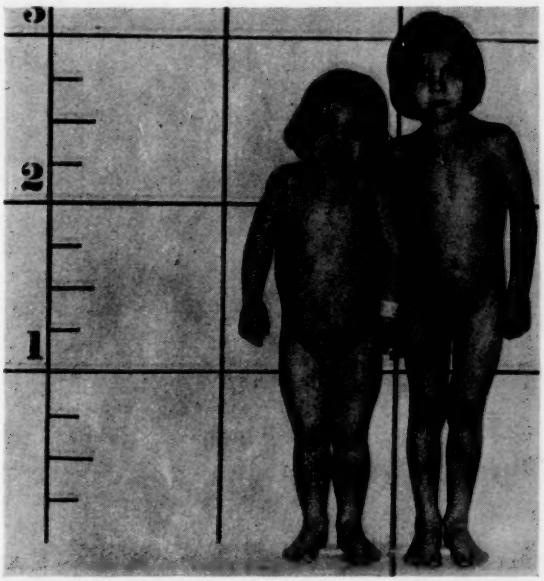

Fig. 5.—(Reprinted with permission of A.M.A. Am. J. Dis. Child.[20])

In Fig. 5, discordant monozygotic twins, aged 4 years, 3 months, are seen. The child on the left is athyroid. At delivery these children appeared indistinguishable. By the age of 3 weeks the athyroid child was noted to be "different" from her twin; her tongue had become large, her skin was "blue and cold," and an umbilical hernia was evident. The cry had become hoarse, she had difficulty with swallowing, and constipation was prominent. The diagnosis of hypothyroidism was made when she was 6 weeks old, and she was treated with desiccated thyroid until the age of 2 years. In response to her initial therapy, major signs of the disorder quickly vanished, but growth did not equal that of the twin.

During a subsequent 2-year lapse of treatment, signs and symptoms reappeared and became pronounced, and differences in growth and body proportionment progressed to the degree shown in the photograph. Her bone age at the time of photographing was only 1 year, 3 months. She was then placed on an adequate program of treatment with Na-l-Thyroxine. Subsequently, all physical and biochemical signs of deficiency have again disappeared, and growth and bone age deficits are now overcome. The more desirable growth and skeletal maturation which accompanied the latter course of treatment with thyroxine and the degree of skeletal retardation and growth failure with her initial treatment indicates that therapy during the first two years was inadequate; this is further evidenced by the fact that she has a significantly lower I.Q. than her euthyroid sibling. As well as demonstrating the physical effects of prolonged hypothyroidism, this case again emphasizes the relationship of adequate therapy during infancy to mental development.

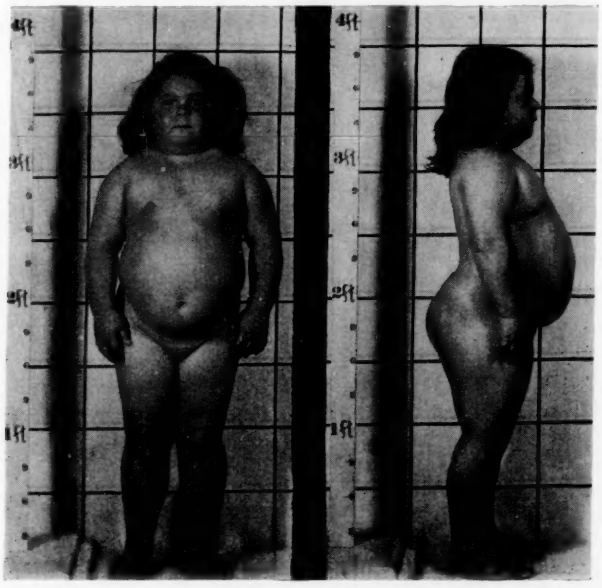

Fig. 6.

In Fig. 6 is seen a girl aged 9½ years in whom signs and symptoms of hypothyroidism dated back to the age of 4½ years when she had a tonsillectomy and removal of a "peculiar mass" (presumably a lingual thyroid) at the base of her tongue. Growth and development until that time were normal. Growth was retarded after surgery. Diagnosis of acquired hypothyroidism was made at the age of 9½ years at which time myxedematous skin changes were marked and macroglossia was moderate. Her voice was hoarse, she described cold intolerance, she had a poor appetite (despite obesity), she was constipated, and she had the ability to drop off to sleep with ease. Her height was considerably below the third percentile. X-ray studies revealed epiphyseal dysgenesis and a bone age of

5½ years (Fig. 9). With diagnosis of acquired hypothyroidism at the age of 9½ years, she was placed on an adequate program of treatment with Na-l-Thyroxine. Physical signs of hypothyroidism rapidly disappeared along with a significant loss of weight. The rate of growth and skeletal maturation increased so that after three years of treatment her weight, height, and bone age were normal. Her I. Q. has always been normal.

X-RAY IN DIAGNOSIS AND THERAPY

Thyroid hormone has a primary role in the process of skeletal growth and maturation. In this laboratory, histopathologic and x-ray studies of athyroid infant rhesus monkeys revealed generalized retardation in development of the skeletons involving both linear and circumferential growth, aging, and bony reconstruction. This applied to all types of ossification in both membranous and enchondral bones. The retardation was most pronounced by delayed skeletal aging and bony reconstruction. Somewhat less affected was enchondral and membranous ossification; periosteal ossification was least affected. These combined factors produced the dwarfed, relatively broader, more dense, more infantile skeleton characteristic of the athyroid animal not unlike that seen in thyroid-deficient human infants and children. These changes were completely prevented by adequate treatment with l-Thyroxine in other experimental animals; however, skeletal retardation persisted in other animals less adequately treated. The latter group showed retarded brain development similar to that observed in the untreated animals.[13,66-69] The clinical association between inadequate treatment and persisting skeletal retardation and mental retardation was first suggested by Wilkins[77] and Brown, Bronstein, and Kraines[5] 1938, and has been discussed.

In a term infant with suspected thyroid deficiency, the lack of ossification of the distal femoral epiphysis (normally appearing at 35 to 40 weeks of gestation) and/or the proximal tibial epiphysis (normally appearing at about 40 weeks of gestation) strongly suggests intrauterine hormone deficiency and placental dysfunction.[69-71] Standards of reference for this age are tabulated in Edith Potter's *Pathology of the Fetus and Newborn*[71] and are graphically presented in J. Caffey's *Pediatric X-ray Diagnosis.*[69]

During the first year of life there is a relatively more rapid appearance of secondary centers of ossification in the foot as compared to the hand and wrist; therefore, a combination of foot, hand, and wrist x-rays are recommended in the initial x-ray evaluation of infants with suspected hypothyroidism. Reference standards for evaluation of postnatal skeletal maturation include those of Stuart[72] for the feet, Gruelich and Pyle[73] for the hand and wrist, and Pyle and Hoerr[74] for the knee. All are compiled on the basis of 3-month standards during the first year.

Between the ages of 2 and 5 years hand and wrist films are usually adequate. It has been our experience that serial x-ray films of the hand and wrist are adequate for follow-up. After the age of 5 or 6 years, when changes in the hand and wrist are less rapid, the addition of knee films and their evaluation according to the atlas of Pyle and Hoerr is helpful.

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Epiphyseal dysgenesis, another characteristic x-ray sign of thyroid deficiency, is commonly seen in the proximal femoral epiphysis. It should not persist if substitution therapy is adequate.[68,75,76]

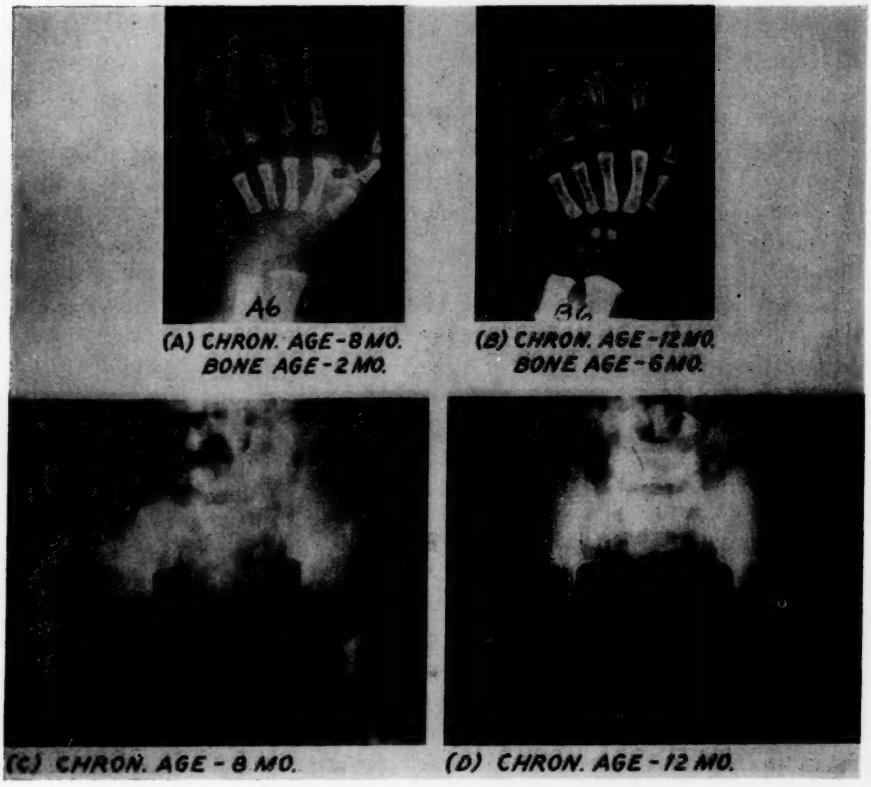

Fig 7.

Clinically, precautions should be exercised to protect the patient against needless irradiation during roentgen study or during treatment in confirmed cases. By using properly calibrated and monitored x-ray equipment, by shielding those parts of the body not involved in the desired exposure (particularly the gonads), and by restricting the number of exposures to the necessary minimum, the patient will gain the benefit of minimal radiation exposure.

Figs. 7, 8, and 9* are presented to emphasize the significance of roentgen evaluation in diagnosis and therapy.

CASE 1 (Fig. 7).—This case was diagnosed when the female cretin was 3 months of age. The child was treated inadequately with desiccated thyroid (15 to 45 mg. per day), until the age of 8 months, when the bone age was two months (*A*). Roentgen examination of the pelvis at that time revealed absence of ossification of the capital femoral epiphyses (*C*), normally present at the age of 8 months. Subsequent treatment with sodium l-Thyroxine (0.15 mg. per day) for

*These x-rays are reprinted with permission from *Radiology*.[68]

4 months resulted in rapid skeletal growth and development so that at 12 months of age the bone age was six months (*B*) and the capital femoral epiphyses were of normal appearance (*D*).

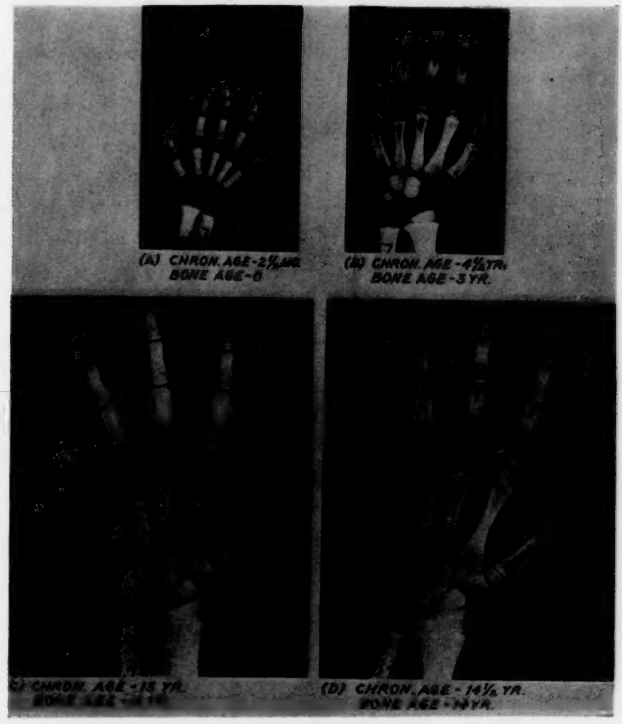

Fig. 8.

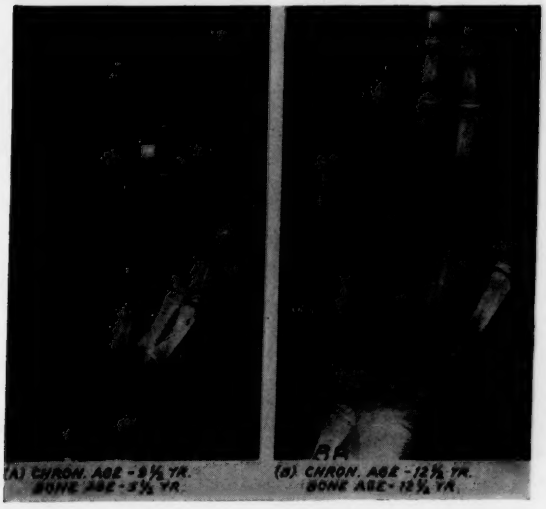

Fig. 9.

CASE 2 (Fig. 8).—These x-rays were selected from studies of a cretin whose case was diagnosed when the patient was 2½ months of age. The bone age was then equivalent to that of a newborn

infant (*A*). Therapy with desiccated thyroid (30 to 60 mg. per day) was instituted and continued until the patient was 4½ years old, at which time the bone age was 3 years (*B*). Thereafter, until the age of 13½ years, the patient received desiccated thyroid in varying doses (90 to 120 mg. per day). Growth, development, and bone age continued to lag (*C*). With institution of optimal sodium l-Thyroxine therapy (0.2 mg. per day), bone development advanced rapidly to normal (*D*), but the patient remained mentally retarded.

CASE 3 (Fig. 9).—These x-rays are of the child described in Fig. 6, who was rendered athyroid by surgery at the age of 4½ years, and whose hypothyroid condition remained undiagnosed until the patient was 9½ years old, at which time the bone age was 5½ years (*A*). Treatment with sodium l-Thyroxine (0.2 to 0.3 mg. per day) brought about an excellent clinical response, with rapid resumption of growth and skeletal development. After 3 years of such therapy the bone age was normal (*B*). The patient was of normal intelligence.

LABORATORY AIDS TO DIAGNOSIS AND THERAPY

Laboratory aids of particular value in confirming suspected hypothyroidism in infants and children include the determination of serum hormonal iodine concentration and the determination of I^{131} uptake by the thyroid. These parameters directly reflect disturbances in thyroid function; in conjunction with the determination of skeletal maturation they represent an adequate means for diagnosis and differentiation of the various types of hypothyroidism in infancy and childhood.

Serum hormonal iodine is routinely determined by one of two basic methods; these are the protein-bound iodine (PBI) method[78-82] and the butyl alcohol extractable iodine (BEI) method.[83-85] The PBI method measures all protein-bound iodine in serum; whereas the BEI method selectively measures thyroxine and tri-iodothyronine and is chemically more accurate. Either determination becomes invalid when children have been given iodinated contrast media for x-ray studies. BEI values are less affected in this regard than are PBI values.[83-86] Administration of inorganic iodides (KI, hydriodic acid, etc.) elevates serum PBI values but not serum BEI values.[85,87]

Lower limits of normal for either method must be interpreted relative to the laboratory involved, method used in the determination, and the age of the patient. The serum hormonal iodine concentration, normally equilibrated with maternal levels at birth, rises significantly to values ranging from 7 to 12 mcg. per cent during early neonatal life and subsequently remains elevated for a fortnight or longer, thence returning to levels common throughout the remainder of infancy and childhood.[42-44,80-85,90] We consider as abnormal serum hormonal iodine concentrations below 6 mcg. per cent for the PBI and below 5 mcg. per cent for the BEI method during the neonatal period. By the age of 1 month, values below 5 and 4.5 mcg. per cent, and after the age of 1 year, values below 4.5 and 4 mcg. per cent for BEI and PBI, respectively, are considered abnormal. In our laboratory the values for serum BEI concentrations in cases of congenital athyrosis have not exceeded 3.5 mcg. per cent and have usually ranged from 0 to 2 mcg. per cent. In sporadic familial goitrous hypothyroidism the depression of serum BEI concentration has paralleled the degree of hypothyroidism, whereas PBI values have often been disproportionately high. In children with this condition the disproportionately high PBI value may lead to a false diagnostic impression and inappropriate therapy. A borderline value calls for a serious re-evaluation of the case. In any infant in whom the suspected diagnosis cannot be satisfactorily

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ruled out, a therapeutic trial of optimal substitution therapy is indicated. During such a program of treatment a successful response would be one in which there occurred definite clinical improvement with acceleration of bone growth and maturation and a significant elevation of serum hormonal iodine concentration.

In therapy, the serum hormonal iodine concentration should be maintained at 6 mcg. per cent or above when Na-l-Thyroxine is used and 5 mcg. per cent or above when thyroid (U.S.P.) is used.

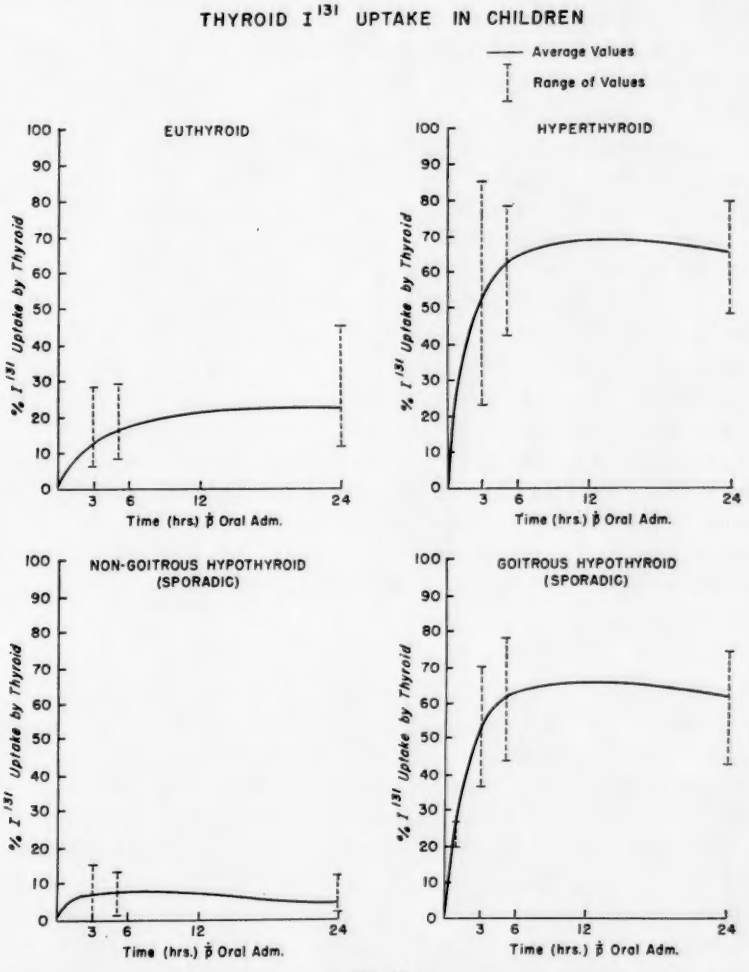

Fig. 10.

Other laboratory determinations may be helpful in the initial evaluation of a child with suspected hypothyroidism. The serum cholesterol concentration is typically elevated beyond the first year of age;[13,90] elevated serum carotene values are common in the hypothyroid infant but are unreliable in older children;[13,14,91] and serum alkaline phosphatase is typically depressed.[92] The basal metabolic rate determination is unreliable in the pediatric age group.

I^{131} uptake by the thyroid is easily determined with administration of a tracer dose of carrier-free radioactive iodine (I^{131}). Modern scintillation detection equipment permits satisfactory investigations with as little as 0.1 μc. of the isotope. If sufficiently sensitive detecting instruments are not available and doses in excess of 5 μc. are needed for a satisfactory study, serious consideration must be given to deferring the study. There is too little definitive information regarding the long-range effects of this isotope to permit an attitude of complacency to accompany its use. In this laboratory the dosage is restricted to less than 0.5 μc. during infancy and early childhood.

The I^{131} accumulation by thyroid is of value in confirming thyroid agenesis and is helpful in differentiating sporadic familial goitrous hypothyroidism (Fig. 10).[25,26,93-95]

Data presented in Fig. 10 include studies conducted on more than 100 children with thyroid abnormalities. The range of per cent of administered I^{131} accumulated by the thyroid gland in euthyroid children is shown and compared to the range of "uptake" observed in hyperthyroid, sporadic athyroid, and sporadic goitrous hypothyroid subjects. The low values in the athyroid group are to be contrasted with the markedly elevated uptakes usually observed in the sporadic goitrous hypothyroid children.

The elevated thyroid I^{131} uptake in the sporadic familial goitrous hypothyroid child is inhibited when such cases are adequately treated with Na-l-Thyroxine. This phenomenon may be of clinical aid in confirming the diagnosis.

In children in whom secondary (pituitary) hypothyroidism is suspected, the measure of I^{131} uptake by thyroid before and after administration of pituitary T.S.H. may be of value. In the majority of such cases there occurs a marked increase in I^{131} uptake following administration of T.S.H. (0.5 μ TSH per kilogram per day in two divided doses daily for 3 days).[93,96]

SUMMARY AND THERAPEUTIC COMMENTS

In the preceding sections of this review particular emphasis has been placed on the significance of adequate thyroid hormone in growth and development of the central nervous system during infancy. Evidence has been presented which suggests that threshold requirements of the central nervous system and skeletal system exceed those of other tissues such as liver, skin, and muscle. Therapy therefore must not be gauged according to the response of the latter tissues.

The dosage of hormone necessary to provide an optimal skeletal response also produces serum hormonal iodine concentrations well within the normal range. Serial determinations of serum hormonal iodine concentrations and serial skeletal x-ray examinations should be performed at sufficiently frequent intervals to insure that the serum concentration of hormone is rapidly attained and maintained well within the normal limits and that skeletal growth and maturation is accelerated to a normal rate. It is also important to conduct psychometric examinations in these children at the time of diagnosis and periodically during therapy.

Commercial preparations available for replacement therapy are Na-l-triiodothyronine, thyroid (U.S.P.), and Na-l-thyroxine.

Use of Na-l-tri-iodothyronine as a therapeutic agent in infants and children is still under investigation. Until such a time as it is proved that this compound is capable of producing a normal growth and development of the central nervous system, we are withholding its use clinically in the athyroid infant. The significant advantage of serial hormonal iodine determinations as a guide to therapy in infants is lost with use of this compound since serum protein does not bind l-tri-iodothyronine and serum hormonal iodine values do not reflect the dose administered.[97-100]

Na-l-Thyroxine and desiccated thyroid are both satisfactory therapeutic agents for treating thyroid deficiency in infants and children. It has been shown that 0.1 mg. Na-l-Thyroxine is approximately equivalent to 90 mg. desiccated thyroid.[101-105] We prefer Na-l-Thyroxine because of its reliable consistency, relative lack of toxicity, and predictable metabolic and growth effects in relationship to the constant serum hormone levels resulting from any given dosage (in the same patient). The desirable clinical and metabolic effects, including normal growth and development of the skeletal system, result from the administration of doses which sustain the serum BEI concentration at values of 6 mcg. per cent or above.[13,46,47]

There appears to be a considerable margin between the therapeutic and toxic range. Toxic signs are rarely observed unless BEI concentration exceeds 12 mcg. per cent. In our clinic, several children who manifested toxicity with relatively inadequate doses of desiccated thyroid fully tolerated adequate doses of thyroxine without toxicity.

From birth to age 8 months, 0.1 to 0.15 mg. Na-l-Thyroxine per day is the average dose required to produce serum BEI values in the range of 6 to 10 mcg. per cent, while a daily dose of 0.15 to 0.20 mg. is the average through the next 8 to 12 months. In older children the dosage is proportionally increased to an average of 0.3 mg. daily by adolescence. These doses and the resulting serum BEI values approximate the daily output of hormone by the thyroid gland in euthyroid subjects.[102-105]

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Editorial

SOME SOCIAL CONSIDERATIONS ABOUT RESEARCH AND PROLONGED HOSPITAL STAY

That the patient's medical condition by itself is not the sole reason for admission or for prolonged residence in general hospitals has long been surmised by many medical professional and administrative workers. Generations of interns, residents, and their teachers have suspected this in their search for interesting medical teaching material. Social workers in hospitals directly involved with the problem have always been acutely aware of it. But organized study on a substantial scale has been undertaken only relatively recently with the more ready availability of funds for this purpose from public health agencies and private philanthropic foundations.

A rapidly growing literature within the past decade reflects the awareness of and interest in the complex problem of chronic illness, the extended duration of stay in general hospitals, and the consequent enormous cost to communities of existing care facilities and the increasing need for their expansion. In a number of published research projects in this country and abroad some appreciation of the relevance of nonmedical aspects of prolonged illness is evident. Included in the survey schedules have been a small number of socioeconomic data, such as age, marital status, income, housing, occupation — hard static facts easily amenable to quantitative measurement. While these data yield some significant information, they do not apparently throw strong enough light upon the basic problem, for they do not always consistently come through in the findings or conclusions. There are other studies, to be sure, which have attempted to penetrate more deeply into other dimensions of the problem, including less tangible and more dynamic items such as home environment, relationships of patient and family, and their attitudes toward the patient's illness and his needs. However, the initial intention to approach this highly relevant aspect of study soon tends to weaken. At an early stage of the survey, the pursuit seems to become abandoned, and the collected data fail to emerge in the analysis, evaluation, or conclusions.

For example, one medical study[1] declares that "a detailed analysis of the social data would go beyond the scope of the present study, and in any event the user of the material must evaluate the data in terms of his own particular interests. Needless to say, it must be borne in mind that any survey which evaluates patients in the hospital will show a concentration of problems far exceeding the picture of morbidity in general population. . . ."

In another medical study[2]: "Social needs were not included in the patient profile, as suitable data were lacking in many instances, and a social inventory

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of patients could not be carried out as part of the study. This made it impossible to determine whether patients who do not require continued hospital care could be adequately cared for at home. When patients were known to social service departments, pertinent information was obtained with the result that some insight into non-medical reasons for hospitalization was gained. . . ."

This latter study carries the implication that the comprehensiveness of its social data did not remotely approach that of medical information. To do so, it was declared that at least an interview with the patient and in selected instances with members of the family as well would be necessary; and an adequate social inventory would be essential if possibilities of home care were to be determined. It was recognized that the needs of individual patients could be more precisely defined if adequate provision were made for collection and analysis of such information but that the collection of these social data would take more time than the accumulation of medical information.

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It would seem from the foregoing examples that when a project undertakes to inquire into the size of the problem for the hospital and community, and into reasons for the prolonged duration of hospitalization, the assumption has apparently been made before initiating the study that the stay there was excessive. Therefore, only limited returns on the investment of time in such studies can be anticipated unless, along with the clinical material, adequate and significant social data are also collected, analyzed, and correlated with the clinical data. Moreover, with the gathering of knowledge about the individual patients there is needed simultaneously some attention to the community and its resources, to ascertain what services other than general hospitals are available or lacking.

In practice there is infinite experience to demonstrate that three different but related social areas have specific bearing on the problem of prolonged illness and its effective treatment: (1) economic, social, and psychologic elements in the patient's own personal life; (2) availability and accessibility of community resources; and (3) structure and policies (administrative and clinical) within the hospital serving the patient. As practical experience points to these three elements as fundamental and interrelated, it should not be unreasonable to expect that research initiated for an understanding of the problem more precisely should include the same elements. Some very limited consideration as suggested earlier in this paper has been given to the first element, that is, the individual patient's own personal situation. But the other two aspects have been generally neglected.

An incident from another study[3] will exemplify the value of the second point. The aim of the study was to determine whether a given medical institution met the community's need for the care of orthopedically handicapped children. An hypothesis held by persons initially stimulating the undertaking of the study had been that prolonged institutionalization of sick children (no matter how good the institution) was deleterious to their best interests. This view reflects a currently held concept generally accepted as sound that separation from his own home or from a substitute home has an adverse effect on a child's growth and development. Some proponents of the study had believed without qualification that there existed in that highly organized community more constructive means

than admission to an institution for providing the needed care; namely, the use of homemaker service in the child's own home or of care in a foster home. Agencies with both types of service were well established in that community.

In the course of the study, with the collection of medical and social data concerning the residents of this medical institution, an inquiry was made concurrently to ascertain whether the presence or lack of needed community resources might have influenced the admission and continued long stay in the institution. What was the nature of the actual relationship between this institution and the other community services? Was there any discrepancy between the current practice of the relevant community agencies and the implication that their mere existence was equated with their availability and accessibility to the particular individual sick children in question? Furthermore, two other lines of study were simultaneously undertaken: a questionnaire to the more than twenty referring hospital, social service departments, and numerous private physicians; and a letter to the major child care agencies and homemaker services in the community in question. The hospitals and physicians were asked to indicate whether they would have preferred some solution to the problem other than institutionalization, and to list in detail any lacks in the community resources needed to carry this out. The child care and homemaker agencies were asked to describe their current policies, to indicate whether patients of this type came within their purview, and, if not, whether any immediately prospective change of policy was contemplated. The prompt 100 per cent return on these inquiries produced a long list of serious community lacks. Moreover, no child care agency was prepared to accept children with these orthopedic handicaps for the length of time required. The policies of all the homemaker services, providing mainly temporary service during a mother's illness, likewise excluded problems of this kind. Thus, the services needed to implement a positive concept of child care which would have rendered many admissions unnecessary or would have reduced the duration of their stay were as unavailable for these patients as if the agencies actually were nonexistent.

Similar circumstances without doubt could be found to exist with regard to adult patients long resident in general hospitals and other institutions. Therefore, a study of individual hospitalized patients only, without concurrent study of existing agency practices within the community, will produce a partial picture of the total situation, and may even result in unrealistic conclusions and recommendations. This should be a problem for joint cooperative community study, planning, and action — both medical and social.

Still another important area for study, with direct bearing on the patient in the general hospital are administrative and clinical policies of the hospital. In one study of reasons for prolonged stay, the medical participant sought to amplify the social information about patients through contact with the social service departments of the four hospitals under study. There was striking variation in the proportions of patients who had been known to the several departments before the study was begun. Whereas only an intensive study of the departments in question might fully explain these differences, the evidence seemed clearly to point to several factors: (1) the size of social service staff in relation to size of hospital, (2) the degree of integration of the social and clinical aspects

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of patient care in general, and (3) the presence or absence of regular periodic systematic structured conferences between clinicians responsible for the care of patients and the social worker assigned to the service. In the hospital with the largest number of long-stay patients a large proportion of them, prior to the study, had never been referred to the social service department by doctors. In this hospital, too, it was found from observation and direct report that the degree of integration of clinical and social services were far less than in two hospitals with small numbers of long-stay patients. Nor did there exist any type of regularly planned medical social conference for the joint review of patient needs by doctor and social worker together.

In the two hospitals with the small number of long-stay patients there have been developed regular conferences or ward rounds specifically focused on ascertaining the total medical social situation of all patients, so that their current care needs could be appropriately served, and that suitable plans for their aftercare could be promptly initiated and carried forward. Numbers of long-stay patients in these two hospitals judged not to need general hospital care were relatively few. Those who did remain in the hospital were there either as part of a deliberate plan on the part of the hospital personnel, or because of obstacles to discharge which could not immediately be resolved without undue hardship to the patient. No patient was there by default, so to speak, because he had been overlooked or forgotten.

Strong clues in the two studies quoted as illustrations earlier in this paper and in other studies suggest the substantial role that adverse social circumstances in patients' lives and inadequacies of community organization play in this problem. But the awareness of this fact is not sufficiently exploited in these or other medical surveys to extend the knowledge of the needed facts and to begin to break down the barriers to effective community action.

There still remain to be identified the reasons for the failure in medical surveys to replace the tentative and token social approach by a more substantial and vigorous study of the nonmedical aspects of chronic illness. At the risk of appearing to be provocative as well as presumptuous in a highly technical field two main reasons suggest themselves, although both do not necessarily always operate simultaneously: (1) difficulty in the objective quantitative measurement of relationships, attitudes, and environment; and (2) insufficient conviction as to the significance of these factors in illness generally or in prolonged illness specifically.

From a lack of firm conviction, adequate time, budget, or personnel are not allotted for the comprehensive consideration of social data during the entire study process — in the preliminary exploratory and planning phases, in the testing out period, and in the period during operation, when continuous correlation and evaluation are essential. For full participation in the study team, the social work profession could be called upon to provide personnel. Because of their first-hand experience with the social problems of sick people, expert knowledge of organized medical care, and of social community organization, qualified social workers have a distinctive contribution to make in studies of this kind.

That social data continue to present difficulties for scientifically oriented research is well recognized. It is conceded also that subjective judgments are inevitable in estimating the nature and quality of interpersonal relationships and intrapsychic phenomena. But is this not true also of all studies dealing with human problems? Do not clinical statements as to degree of illness, prognosis, and rehabilitation potential similarly have a high degree of subjectivity determined by judgment, skill, and clinical orientation? However, this does not prevent the inclusion of such statements in clinical surveys. Usually some acknowledgement is made of the difficulties this presents for strictly quantitative study and for repeatability of experience, and every effort is made in study design to reduce the probability of error introduced in this way. But, the important thing is that the problem is faced.

To what degree social data will ever yield to approved biostatistical methods cannot now be readily predicted. But this problem too must be faced. Every opportunity should be given in clinical surveys for experimentation with methodology in the use of relevant interrelated social material. New techniques different from those currently in use may be developed. The present barrier may yet be broken, and the inclusion of relevant social elements to validate clinical and administrative studies in this field may become imperative even for those presently unconvinced.

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Book Reviews

ORTHOPEDICS FOR THE GENERAL PRACTITIONER. By William E. Kenney, M.D., and Carroll B. Larson, M.D., F.A.C.S. St. Louis, 1957, The C. V. Mosby Co. Pp. 413. Indexed. Price $11.50.

This book was designed to help the general practitioner in his orthopedic problems, lighten his burden, and make his professional life happier through a fuller understanding of this special branch of medicine. The book is designed as a reference for the physician in as much as it is organized on the basis of the anatomic location of the deformity or disease described. It is divided into two areas—the diseases in childhood and those associated with the adult. This book would certainly appear to be useful not only in the library of the general practitioner and the pediatrician, but may also find a place in the library of the medical student, the intern, and the assistant resident who is interested in or has to cope with orthopedic problems. The book is clearly written, the illustrations are pertinent, and it is not overly long. The general practitioner can quickly find the information that he desires and needs in this book due to its organization and clarity.

Robert A. Robinson

AN INVESTIGATION INTO THE VOCATIONAL POTENTIALS OF HOSPITALIZED PATIENTS WITH CHRONIC DISABILITIES. First, Second, and Third Semi-Annual Progress Reports. Chief Investigator, Mieczyslaw Peszczynski, M.D. Department of Physical Medicine and Rehabilitation, Highland View Cuyahoga County Hospital, Cleveland, Ohio. Mimeographed, 233 pages. (Available free on request from above-mentioned hospital.)

A cardinal goal of medical treatment is the return of the patient to his community, capable of caring for himself and his family. Where this goal is not achieved, patients accumulate in nursing homes, chronic disease hospitals, and infirmaries. This volume records the beginning of a five-year project to find reliable methods of selecting from a group of chronic patients those who will succeed in industrial employment. Facilities are available not only to evaluate patients and to place them in industry, but also to follow their progress and compare it with predictions. The work underway includes exploration of the patient's physical, emotional, and mental status, investigation of job opportunities open to disabled persons, examination of how tools and equipment can be modified to the patient's disability, and study of how the transition from the hospital to industry may be improved.

The exact responsibility of each member of the staff and his relation to other members is described in some detail. The staff consists of a physiatrist, two occupational therapists, one psychologist, two vocational counselors, a manual arts instructor, a shop supervisor, and a representative to investigate and arrange employment possibilities.

It is too early yet to have reached any conclusions. One interesting problem has been the inability of many patients in the hospital with chronic diseases to consider themselves responsible for helping themselves. They are so preoccupied with their own disabilities that they see no reason to work. Such an attitude defeats any attempt at rehabilitation and poses a real question as to how many can be permanently located in industrial jobs. At the end of five years we will hope to know how effective the program has been in terms of numbers of patients actually in industrial work, the costs of such a program, and the techniques for selection of successful workers.

Douglas Carroll

CHOLESTERIN-ERNÄHRUNG-GESUNDHEIT. (Cholesterol, Nutrition, Health) By Univ.-Prof. Dr. Wilhelm Halden, F.A.P.H.A., Graz and Univ.-Dozent Dr. Ludwig Prokop, Wien. Pp. VIII & 80, with 16 illustrations and 20 tables. München, Berlin, Wien, 1957, Urban & Schwarzenberg. Price DM 9.

Research on the relationship between the diet, cholesterol metabolism, and coronary heart disease is currently so intensive and progress so rapid that there is a special need for up-to-the-minute reviews. Professor W. Halden and Doctor L. Prokop have, surprisingly, supplied the best of such reviews now available in their small monograph, "Cholesterin, Ernährung, Gesundheit." The word "surprisingly" is provoked because research activity on this subject has been concentrated in countries other than Austria, especially in the United States, and the majority of the recent literature is in English, not in German. But Halden and Prokop are well informed, and they bring to their task a certain detachment that is difficult to achieve for writers closer to the center of research action.

The authors do not arrive at conclusions different from those held by many workers in the thick of the field but it is of some consequence that they started from an independent position and reached their judgments without the pressures of personal justification that inevitably act on researchers whose views have been progressively committed to print in series of papers extending over the years. New entrants to a field of research controversy are uncommitted to previous interpretations.

Writing from central Europe, Halden and Prokop naturally have more familiarity with the European literature than do American workers and their monograph is particularly useful for the citations to papers in languages other than English. It is heartening to find in their references so many indications that medical research on the European continent is emerging from the long blight of war, political interference, and poverty.

Halden and Prokop devote relatively little space to discussion of the findings in experiments on animals. The large literature from studies on rabbits, chicks, and other laboratory animals was well covered up to about five years ago in the monograph by Louis Katz and Jeremiah Stamler, "Experimental Atherosclerosis," and the subsequent developments, though important, have not greatly changed that picture. And, as Halden and Prokop point out, the extrapolation to man of findings on cholesterol metabolism and atherogenesis in animals must be made with great caution. So far, at least, the transfer of interest from the rabbit and the chick to other species, including monkeys and pigs as well as dogs and rats, seems mainly to have demonstrated further the differences between species and the fact that the precise equivalent of human coronary heart disease, pathologically and etiologically, may not be produced readily in animals.

Though the authors can scarcely be criticized for their scanty attention to the evidence from animals, it is possible to find fault in their lack of interest in the statistical evaluation of evidence, both in human experiments and in studies on populations. They cite the evidence but not always critically. In this respect their attitude is typical of most medical research on the European continent and, for that matter, the majority of research that is clinically oriented in the United States. Some of the apparent conflicts in the evidence they cite would disappear, or at least be lessened, if more attention were paid to the relative validity of different investigations as indicated by the use of controls, adequate numbers, and statistical analysis of the results.

But the net result is a valuable compendium of data accurately reported and a logical development of conclusions which are conservatively stated. There is clear recognition of the implications for public health applications in the future and a set of recommendations that will not arouse violent controversy if they are accepted for what they are—tentative and interim suggestions for the clinician who must adopt some regimen for his patients now without waiting for all the scientific facts to fall into neat order.

Ancel Keys

TRENDS IN GERONTOLOGY. By Nathan W. Shock, Ph. D. Ed. 2, Stanford, Calif., 1957, Stanford University Press, Price $4.50.

Few medical publications go into a second edition, and when one does, it is a significant indication of its excellence and durability. This second edition of *Trends in Gerontology* has been

rewritten, rather than revised, to encompass the recent phenomenal development of both research and action programs in the field of gerontology. The author is a well-known authority in this field with a wide knowledge of his subject and a clear and trenchant style.

The chapters cover population trends, problems of unemployment and retirement, income, health, living arrangements, and education, community, and research programs in relation to older people. The book is well provided with carefully selected charts and tables. There is a description of medical centers throughout the world where research on problems of aging are being conducted. The last chapter, entitled "Recommendations: An Institute of Gerontology," outlines the need for a comprehensive approach to the problem of aging and gives a detailed plan of organization. Such an institute would be concerned with the study of the general biology of aging, physiologic and psychologic aspects of human aging, clinical and socioeconomic problems of an aging population.

The comprehensiveness and clarity of the presentation make this book equally suitable for the physician and the layman. It is recommended to anyone dealing with aged people, whether from a medical, economic, financial, or sociologic viewpoint.

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PRIMER FOR PARAPLEGICS AND QUADRIPLEGICS. The Institute of Physical Medicine and Rehabilitation. New York, 1957. Pp. 36. Price $.50

This little booklet is written in language that can be understood by patients and their families. It explains the facts about the disability which occurs with spinal cord injury. It is a well-written manual which should help patients with these disabilities and should help their families understand what has happened to the patient and what he must do about it. At the same time, it tells the patient practical methods of bowel and bladder training and his part in it, what he must do to prevent pressure sores or decubitus ulcers, why and what kind of activity is important, and how to care for his wheelchair and his braces. The information is all practical and should prove very helpful to the spinal cord injury patient in forming good habits in his daily life.

In addition to the discussion of the specific problems a paraplegic or quadriplegic patient must face, there is a section on the vocational rehabilitation program written by Mary E. Sweitzer. There is also a section on the National Paraplegic Foundation and how this organization and others can help the spinal cord injury patient resume life in his community and, if possible, his life at work. The manual was prepared by Dr. Seymour S. Bluestone, now Director of the New York State Rehabilitation Hospital with the assistance of the senior faculty members of the Department of Physical Medicine and Rehabilitation of New York University College of Medicine.

This publication should also be most useful for many workers in a hospital setting who have to deal with spinal cord injury patients and their families.

Copies of *Primer for Paraplegics and Quadriplegics* can be purchased for fifty cents from the Institute of Physical Medicine and Rehabilitation, 400 E. 34th St., New York 16, N. Y.

Florence Mahoney